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(54) Title: BENZ-1,3-AZOLE DERIVATIVES AND THEIR USES AS HEPARANASE INHIBITORS

(57) Abstract: The invention provides benz-1,3-azole derivatives, namely benzimidazole, benzoxazole and benzthiazole derivatives as heparanase inhibitors suitable for treatment of diseases and disorders caused by or associated with heparanase catalytic activity such as cancer, inflammatory disorders and autoimmune diseases.

BENZ-1,3-AZOLE DERIVATIVES AND THEIR USES AS HEPARANASE INHIBITORS

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to heparanase inhibitors, particularly to certain benz-1,3-azoles, more particularly to benzimidazole, benzoxazole and benzothiazole derivatives, and to their use in the treatment of diseases and disorders caused by or associated with heparanase catalytic activity such as cancer, inflammatory disorders and autoimmune diseases.

Heparan sulfate proteoglycans (HSPGs) are ubiquitous macromolecules associated with the cell surface and with the extracellular matrix (ECM) of various tissues. They consist of a protein core to which several linear heparan sulfate (HS) chains are covalently attached. Studies on the involvement of ECM molecules in cell attachment, growth and differentiation revealed a central role of HSPGs in embryonic morphogenesis, angiogenesis, neurite outgrowth, tissue repair, and metastasis. HSPGs are also prominent components of blood vessels. In capillaries they are found mainly in the subendothelial basement membrane, where they support proliferating and migrating endothelial cells and stabilize the structure of the capillary wall.

Several cellular enzymes such as collagenase IV, plasminogen activator, cathepsin B, and elastase are thought to be involved in the degradation of basement membrane. Another enzyme of this type is heparanase, an endo-β-D-glucuronidase that cleaves HS at specific intrachain sites (Nakajima et al., 1984). Heparanase released from cells removes HS molecules from the basement membrane resulting in increase of basement membrane permeability. Heparanase also facilitates proteolytic degradation of the core structural components such as type IV collagen in collaboration with gelatinases. Thus, blood-borne cells accomplish penetration through the basement membrane. In fact, HS catabolism is observed in wound repair, inflammation, and in diabetes.

Expression of heparanase was found to correlate with the metastatic potential of mouse lymphoma (Vlodavsky et al., 1983), fibrosarcoma and melanoma cells (Nakajima et al., 1988). Similar correlation was observed in human breast, colon, bladder, prostate, and liver carcinomas (Vlodavsky et al., 1999). Moreover, elevated levels of heparanase were detected in sera of metastatic tumor bearing animals (Nakajima et al., 1988) and of cancer patients, in urine of highly metastatic patients (Vlodavsky et al., 1997), and in tumor biopsies (Vlodavsky et al., 1988). Treatment of experimental animals with heparanase substrates or inhibitors (e.g., non-

patients, in urine of highly metastatic patients (Vlodavsky et al., 1997), and in tumor biopsies (Vlodavsky et al., 1988). Treatment of experimental animals with heparanase substrates or inhibitors (e.g., non-anticoagulant species of low molecular weight heparin and polysulfated saccharides) considerably reduced the incidence of lung metastases induced by B16-F10 melanoma, pancreatic adenocarcinoma, Lewis lung carcinoma, and mammary adenocarcinoma cells (Vlodavsky et al., 1994; Nakajima et al., 1988; Parish et al., 1987; Lapierre et al., 1996), indicating that heparanase inhibitors may inhibit tumor cell invasion and metastasis.

Heparanase is involved also in primary tumor angiogenesis. Most primary solid tumors (1-2 mm diameter) obtain their oxygen and nutrient supply through a passive diffusion from pre-existing blood vessels, however the increase in their mass beyond this size requires angiogenesis. Heparin-binding polypeptides such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are highly mitogenic for vascular endothelial cells, and are among the most potent inducers of angiogenesis. bFGF has been extracted from the subendothelial ECM produced in vitro, and from basement membranes of cornea, suggesting that ECM may serve as a reservoir for bFGF. Immunohistochemical staining revealed the localization of bFGF in basement membranes of diverse tissues and blood vessels. bFGF binds to HSPG in the ECM and can be released in an active form by HS-degrading enzymes. Heparanase expressed by platelets, mast cells, neutrophils, and lymphoma cells was found to be involved in the release of active bFGF from ECM and basement membranes, suggesting that heparanase activity may not only function in cell migration and invasion, but may also elicit an indirect neovascular response (Elkin et al., 2001).

Heparanase catalytic activity correlates with the ability of activated cells of the immune system to leave the circulation and elicit both inflammatory and autoimmune responses. Interaction of platelets, granulocytes, T and B lymphocytes, macrophages, and mast cells with the subendothelial ECM is associated with degradation of HS by heparanase (Vlodavsky et al., 1992). The enzyme is released from intracellular compartments (e.g., lysosomes, specific granules) in response to various activation signals (e.g., thrombin, calcium ionophore, immune complexes, antigens, mitogens), suggesting its regulated involvement in inflammatory sites and in autoimmune diseases. Indeed, treatment of

experimental animals with heparanase substrates (e.g., non-anticoagulant species of low molecular weight heparin) markedly reduced the incidence of experimental autoimmune encephalomyelitis (EAE), adjuvant arthritis and graft rejection, indicating that heparanase inhibitors may inhibit autoimmune and inflammatory diseases (Lider et al., 1989).

Heparanase inhibitors have been proposed for treatment of human metastasis, for example, derivatives of siastatin B (Nishimura et al., 1994; Kawase et al., 1995), a pyran derivative isolated from the fungal strain *Acremonium* sp. MT70646 (PCT/KR00/01493), suramin, a polysulfonated naphthylurea (Nakajima et al., 1991), sulfated oligosaccharides, e.g., sulfated maltotetraose and maltohexaose (Parish et al., 1999), and sulfated polysaccharides (Parish et al., 1987; Lapierre et al., 1996).

U.S. Patent No. 5,968,822 discloses a polynucleotide encoding a polypeptide having heparanase catalytic activity and host cells, particularly insect cells, expressing said polypeptide. The recombinant polypeptide having heparanase activity is said to be useful for potential treatment of several diseases and disorders such as wound healing, angiogenesis, restenosis, inflammation and neurodegenerative diseases as well as for development of new drugs that inhibit tumor cell metastasis, inflammation and autoimmunity. International Patent Publication No. WO 99/57244 of the present applicants discloses bacterial, yeast and animal cells and methods for overexpressing recombinant heparanase in cellular systems. U.S. Patent No. 6,190,875, assigned to the present applicants, discloses methods of screening agents inhibiting heparanase catalytic activity and hence potentially inhibiting tumor metastasis, autoimmune and inflammatory diseases which comprises interacting a native or recombinant heparanase enzyme with a heparin substrate in the presence or absence of an agent and determining the inhibitory effect of said agent on the catalytic activity of said heparanase enzyme towards said heparin substrate. Both U.S. 5,968,822 and U.S. 6,190,875 and further WO 99/57244 are herein incorporated by reference in their entirety as if fully disclosed herein.

None of the above-mentioned publications and patents discloses or suggests the heparanase inhibitors of the present invention.

SUMMARY OF THE INVENTION

The present invention provides, in one aspect, a pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one heparanase inhibitor selected from a benz-1,3-azole of the general formula I hereinafter.

The pharmaceutical composition of the invention is particularly useful for the treatment of diseases and disorders caused by or associated with heparanase catalytic activity such as cancer, inflammatory disorders and autoimmune diseases.

The heparanase inhibitors used in the pharmaceutical compositions of the present invention are benzimidazole, benzoxazole and benzothiazole derivatives of the general formula I hereinafter.

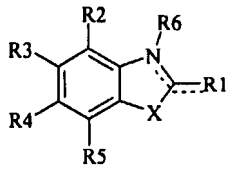
In another aspect, the present invention relates to the use of a benzimidazole, benzoxazole or benzothiazole derivative of the general Formula I for the manufacture of pharmaceutical compositions. In one embodiment, the compositions are for treatment of diseases and disorders caused by or associated with heparanase catalytic activity such as cancer, inflammatory disorders and autoimmune diseases.

In a further aspect, the present invention provides certain novel benzimidazole, benzoxazole and benzothiazole derivatives of the general Formula I.

In still another aspect, the present invention relates to a method for treatment of a patient suffering from a disease or disorder caused by or associated with heparanase catalytic activity such as cancer, an inflammatory disorder or an autoimmune disease, which comprises administering to said patient an effective amount of a benzimidazole, a benzoxazole or a benzothiazole derivative of the general Formula I.

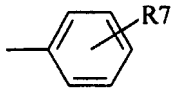
DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, pharmaceutical compositions are provided for treatment of diseases and disorders caused by or associated with heparanase catalytic activity, said compositions comprising a pharmaceutically acceptable carrier and at least one heparanase inhibitor which is a benz-1,3-azole of the general Formula I:

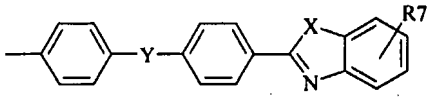


(I)

wherein R1 is a radical selected from a radical (a)-(i) below:



(a)



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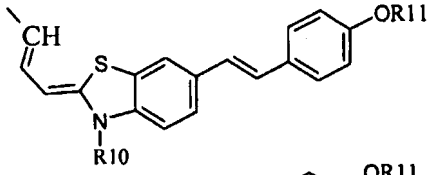

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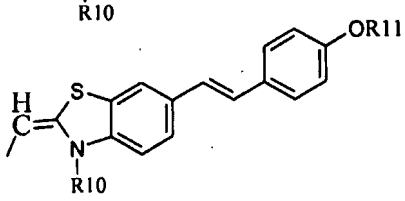

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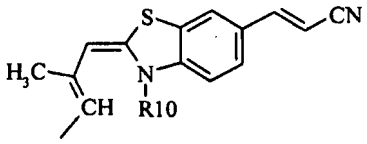

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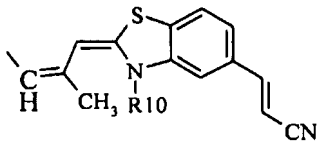

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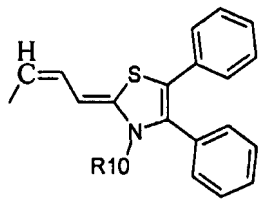
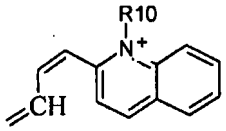
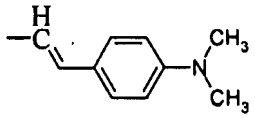


(g)



(h)



(i)

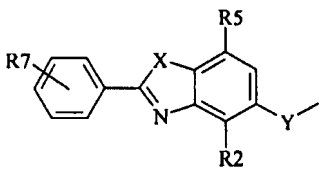
wherein

R2 and R5 each independently represents hydrogen; halogen; -SO_3H; C1-C6 alkoxy optionally substituted by halogen or -SO_3H; C2-C6 alkenyl; C2-C7 alkanoyl; C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; C1-C6 alkylthio; or C6-C14 aryl;

R3 and R4 each independently represents hydrogen, methyl, ethyl, methoxy, ethoxy, nitro, -CH=CH-CN, or -NR8R9;

or R2 and R3 are both H and R4 and R5 together with the carbon atoms to which they are attached form a condensed benzene ring; or R4 and R5 are both H and R2 and R3 together with the carbon atoms to which they are attached form a condensed benzene ring;

or R3 is H and R4 is a radical of the formula (j):



(j)

and wherein in all formulas above:

X is NH, O or S;

Y is a direct bond, -CH_2-, -O-, -CO-, -SO-, -SO_2- or -NR', where R' is C1-C6 alkyl optionally substituted by halogen, preferably fluoro, C2-C6 alkenyl or C6-C14 aryl;

R6 is absent or is C1-C6 alkyl or C2-C6 alkenyl, wherein said C1-C6 alkyl may optionally be substituted at the terminal carbon atom by –NR8R9 or -COOR, where R is H, C1-C6 alkyl, C2-C6 alkenyl or C6-C14 aryl;

R7 is hydrogen or at least one group selected from (i) halogen; (ii) nitro; (iii) -NR8R9; (iv) -SO_3H; (v) -OR12; (vi) -SR12; (vii) C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; (viii) C2-C6 alkenyl; (ix) C2-C7 alkanoyl; (x) C6-C14 aryl; (xi) –N=N-R" where R" is heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S and being optionally substituted by at least one radical selected from -OH, -COOH or -SO_3H; (xii) benzimidazol-2-yl; (xiii) benzthiazol-2-yl; or (xiv) benzoxazol-2-yl, said radicals (xii), (xiii) and (xiv) being optionally substituted by at least one radical selected from halogen, -NR8R9, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, C2-C7 alkanoyl, or C1-C6 alkoxy;

R8 and R9 each independently represents hydrogen or C1-C6 alkyl; or R8 is H and R9 is C2-C7 alkanoyl or C7-C15 aroyl optionally substituted by oxo, -SO_3H, -COOH, and/or -NH_2; or the radicals R8 and R9, together with the N atom to which they are attached, form a saturated 5-7 membered heterocyclic ring optionally containing at least one further heteroatom selected from O, S and/or N, said further N atom being optionally substituted by C1-C6 alkyl;

R10 is hydrogen; C1-C6 alkyl optionally substituted at the terminal carbon atom by -COOR wherein R is H, C1-C6 alkyl, C2-C6 alkenyl or C6-C14 aryl;

R11 is C1-C6 alkyl optionally substituted by fluoro; C1-C6 alkoxy; C1-C6 alkylthio; or -COOR wherein R is H, C1-C6 alkyl, C2-C6 alkenyl or C6-C14 aryl;

R12 is C1-C6 alkyl or C2-C6 alkenyl;

and wherein the dotted lines indicate either a double bond stretching from the carbon atom at the 2 position of the benz-1,3-azole ring to the N atom at the ring, in which case said N atom is positively charged when R6 is present, or the dotted line represents a double bond

stretching from the carbon atom at the 2 position of the benz-1,3-azole ring to the first carbon atom of R1;

and pharmaceutically acceptable salts thereof.

As used herein the term "C1-C6 alkyl" typically refers to a straight or branched alkyl radical having 1-6 carbon atoms and includes for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-heptyl, 2,2-dimethylpropyl, n-hexyl and the like. Preferred alkyl groups are methyl and ethyl. The term "C2-C6 alkenyl" refers to straight or branched hydrocarbon radicals having 2-6 carbon atoms and one, preferably a terminal, double bond, and includes for example vinyl, prop-2-en-1-yl, but-3-en-1-yl, pent-4-en-1-yl, and hex-5-en-1-yl.

The terms "C1-C6 alkoxy", "C1-C6 alkylthio" and "C2-C7 alkanoyl" refer to groups C1-C6 alkyl-O-, C1-C6 alkyl-S- and C1-C6 alkyl-CO-, wherein C1-C6 alkyl is as defined above. Examples of alkoxy are methoxy, ethoxy, hexoxy and the like, examples of alkylthio are methylthio, ethylthio and propylthio, and the like, and examples of alkanoyl are acetyl, propanoyl, butanoyl and hexanoyl.

The term "C6-C14 aryl" refers to an aromatic carbocyclic group having 6 to 14 carbon atoms consisting of a single ring or multiple condensed rings such as phenyl, naphthyl, and phenanthryl optionally substituted by C1-C6 alkyl. The term "C7-C15 aroyl" refers to a group C6-C14 aryl-CO where aryl is as defined above and is optionally substituted by oxo, $-SO_3H$, -COOH and/or $-NH_2$. Examples are 9-oxofluoren-3-oyl, 2-carboxybenzoyl and 2-sulfobenzoyl. The term "heteroaryl" refers to a monocyclic, bicyclic or tricyclic heteroaromatic group containing one to three heteroatoms selected from N, O and/or S such as, but not limited to, pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, quinolinyl, thiazolyl, pyrazolyl, quinazolinyl, 1,3,4-triazinyl, 1,2,3-triazinyl, benzofuryl, isobenzofuryl, indolyl, imidazo[1,2-a]pyridyl, benzimidazolyl, benzthiazolyl and benzoxazolyl.

The term "halogen" refers to fluoro, chloro, bromo or iodo.

The group -NR8R9 may be $-NH_2$, when R8 and R9 are both hydrogen, or secondary amino when R8 is H and R9 is C1-C6 alkyl or tertiary amino when R8 and R9 are each C1-C6 alkyl. The group –NR8R9 may also be a carboxamido group when R8 is hydrogen and R9 is a C2-C7 alkanoyl or C7-C15 aroyl group as defined above, or R8 and R9 together with the nitrogen atom to which they are attached may form a saturated, preferably a 5- or 6-

membered, heterocyclic ring, optionally containing 1 or 2 further heteroatoms selected from nitrogen, oxygen and/or sulfur. Such rings may be substituted, for example with one or two C1-C6 alkyl groups, preferably at a further N atom. Examples of such rings include, without being limited to, pyrrolidino, piperidino, morpholino, thiomorpholino, diazepino, piperazino, and N-C1-C6 alkylpiperazino, e.g. N-methylpiperazino.

Also contemplated by the present invention are pharmaceutically acceptable salts of the compounds of formula I, both salts formed by any carboxy or sulfo groups present in the molecule and a base as well as acid addition and/or base salts.

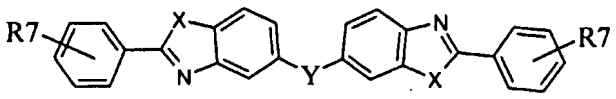
Pharmaceutically acceptable salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge S. M., et al., "Pharmaceutical Salts," (1977) J. of Pharmaceutical Science, 66:1-19). The salts can also be pharmaceutically acceptable quaternary salts such as a quaternary salt of the formula –NRR'R" + Z' wherein R, R'and R" each is independently hydrogen, alkyl or benzyl and Z is a counterion, including chloride, bromide, iodide, O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate.

Pharmaceutically acceptable acid addition salts of the compounds include salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, phosphorous, and the like, as well as salts derived from organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate or galacturonate (see, for example, Berge S. M., et al., "Pharmaceutical Salts," (1977) J. of Pharmaceutical Science, 66:1-19).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

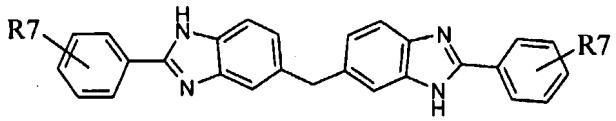
The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

In one preferred embodiment of the present invention, the pharmaceutical composition comprises a compound of the general Formula I wherein R1 is a radical of the formula (a), R2, R3 and R5 are H and R4 is a radical (j), exemplified by a compound of the formula Ia:



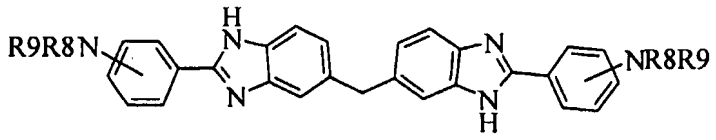
(Ia)

wherein the radicals X, Y and R7 are as described above. According to this embodiment, Y may be $-CH_2-$ and X may be –NH-, thus obtaining a compound of the formula Ib:



(Ib)

In the formula Ib, R7 is preferably -NR8R9, as identified in the formula Ic below:

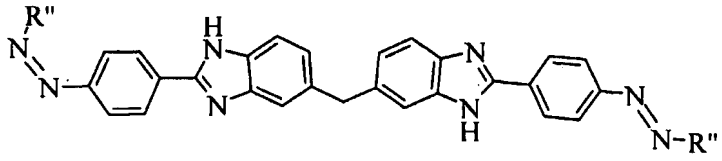


(Ic)

wherein R8 and R9 are as defined above. In one preferred embodiment, in a compound of formula Ic, when -NR8R9 is $-NH_2$ at the para position, there is obtained the compound herein identified as **Compound 1** in the Appendix A just before the Claims. This compound is described in the literature [Hamciuc et al., (1993); CAS No. 47733-85-7] but no biological activity is disclosed for it.

In another preferred embodiment, in the compound of formula Ic, R8 is H and R9 is benzoyl substituted at the ortho position by $-SO_3H$ or -COOH, or R9 is a 9-oxo-fluoren-3-oyl radical, as exemplified by the novel compounds herein designated **Compounds 2-4**, respectively, which structural formulas are depicted in the Appendix A just before the Claims.

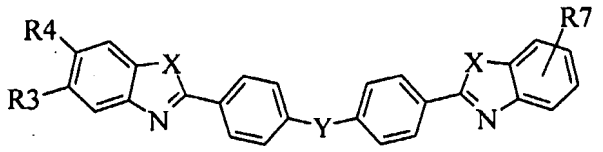
In a further preferred embodiment, the pharmaceutical composition comprises a compound of formula Ia wherein R7 is a radical of the formula –N=N-R", wherein R" is heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S and being optionally substituted by OH, COOH and/or SO_3H, and has the formula Id:



(Id)

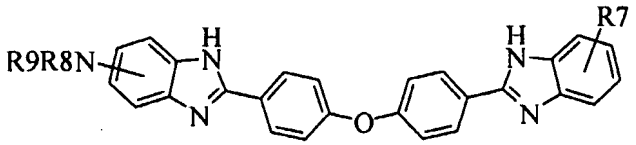
According to this embodiment, R" is preferably a quinoline residue substituted both by OH and SO_3H such as the 5-sulfo-8-hydroxyquinolin-7-yl group, as exemplified by the novel compound herein identified as **Compound 5** in the Appendix A just before the Claims.

In another preferred embodiment of the present invention, the pharmaceutical composition comprises a compound of general Formula I wherein R1 is a radical of the formula (b) such as the compound of the formula Ie:



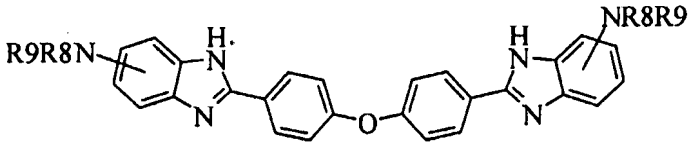
(Ie)

wherein X, Y and R7 are as described hereinbefore and R3 is H and R4 is –NR8R9 or R4 is H and R3 is –NR8R9. Preferably Y is O and X is NH, as is depicted in formula If:



(If)

In a preferred embodiment, in the compound of formula If, R7 is -NR8R9, as depicted in formula Ig:

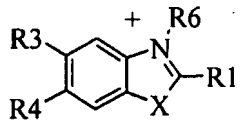


(Ig)

In one preferred embodiment, when in the compound of formula Ig –NR8R9 is $–NH_2$ at the 5-position of the imidazole rings, the compound is herein identified as **Compound 6** in the Appendix A just before the Claims. This compound is described in the literature [Russian Patent Application No. 2027701 (1995); CAS No. 48229-39-6] but no biological activity is disclosed for it.

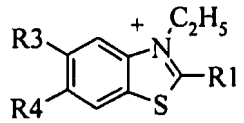
In another preferred embodiment, when in the compound of formula Ig R8 is H and R9 is benzoyl substituted at the ortho position by $-SO_3H$, the novel compound is herein identified as **Compound 7** in the Appendix A just before the Claims.

In another embodiment of the present invention, the pharmaceutical composition comprises a compound of the general Formula I wherein R2 and R5 are H, R6 is C1-C6 alkyl and there is a double bond between the carbon atom at position 2 and the ring N atom such as the compound of formula Ih:



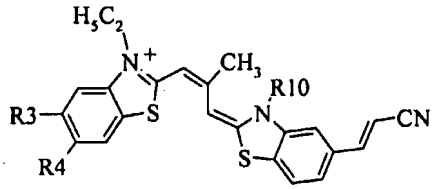
(Ih)

In one embodiment, in the compound of formula Ih, X is S and R6 is ethyl, as depicted in the formula Ii:



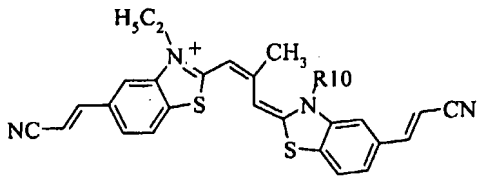
(Ii)

In the formula Ii, R1 may be a radical of formula (f) as in the formula Ij:



(Ij)

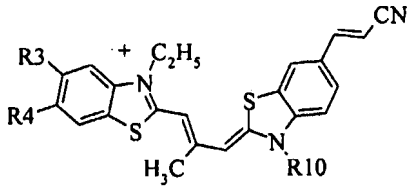
In one preferred embodiment in compound of the formula Ij, R3 is –CH=CH-CN and R4 is H, as depicted by the formula Ik:



(Ik)

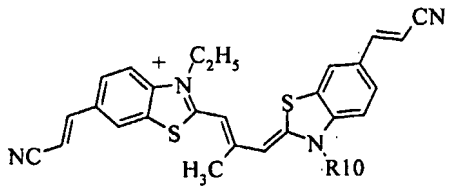
In a preferred embodiment, in formula Ik R10 is ethyl, as exemplified by the compound herein designated **Compound 8** in the Appendix A just before the Claims. This compound is described in the literature [CAS No. 109068-02-2] but no biological activity has been disclosed for the compound.

In yet another embodiment, the pharmaceutical composition of the present invention, comprises a compound of the formula Ii wherein R1 is a radical of formula (e) as in the formula Il:



(Il)

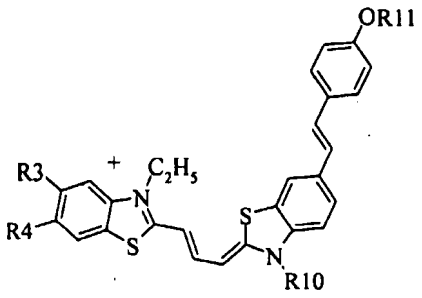
In one preferred embodiment, in the compound of formula Il, R4 is –CH=CH-CN, and R3 is H, as depicted by the formula Im:



(Im)

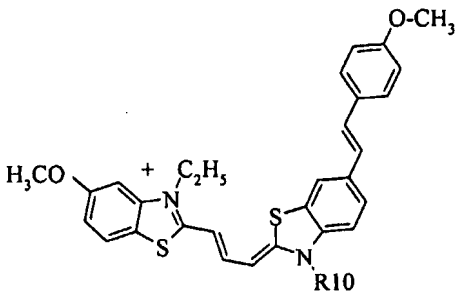
In one preferred embodiment, in the compound of formula Im, R10 is ethyl, exemplified by the compound herein designated **Compound 9** in the Appendix A just before the Claims. This compound is described in the literature [CAS No. 109068-03-3] but no biological activity has been disclosed for the compound.

In another preferred embodiment, the pharmaceutical composition comprises a compound of the formula Ii wherein R1 is a radical of formula (c), as depicted in formula In:



(In)

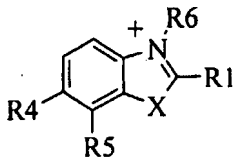
According to this embodiment, when R4 is H and R3 and R11 are both methoxy, a compound is obtained as depicted in formula Io:



(Io)

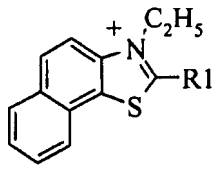
In a preferred embodiment, in the compound of formula Io, R10 is ethyl, as exemplified by the novel compound herein designated **Compound 10** in the Appendix A just before the Claims.

In still another embodiment of the present invention, the pharmaceutical composition comprises a compound of the general Formula I wherein R2 and R3 are hydrogen, R6 is C1-C6 alkyl and there is a double bond between the carbon atom at position 2 and the ring N atom such as the compound of formula Ip:



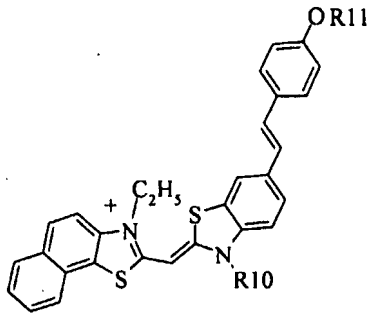
(Ip)

In one preferred embodiment, in the formula Ip, X is S, R4 and R5 together with the carbon atoms to which they are attached form a condensed benzene ring, and R6 is ethyl, as depicted in formula Iq:



(Iq)

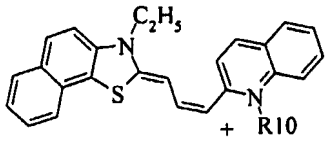
According to this embodiment, R1 may be a radical of formula (d), as in the compound of the formula Ir:



(Ir)

In one preferred embodiment, in the compound of formula Ir, R10 is ethyl and R11 is methyl, as exemplified by the compound herein designated **Compound 11** in the Appendix A just before the Claims. This compound is described in the literature [CAS No.108722-12-9] but no biological activity has been disclosed for the compound.

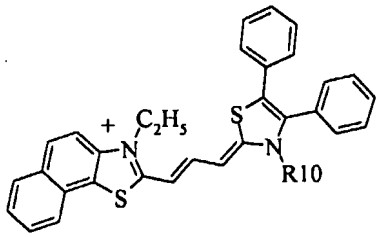
In another embodiment of the present invention, the pharmaceutical composition comprises a compound of the general Formula I wherein R6 is C1-C6 alkyl and there is a double bond between the carbon atom at position 2 of the benz-1,3-azole ring and the first carbon atom of the R1 radical. In a preferred embodiment, R2 and R3 are hydrogen, R4 and R5 together with the carbon atoms to which they are attached form a condensed benzene ring and R1 is a radical of the formula (h), as exemplified by formula Is:



(Is)

According to this embodiment, R10 may be ethyl, as exemplified by the novel compound herein designated **Compound 12** in the Appendix A just before the Claims.

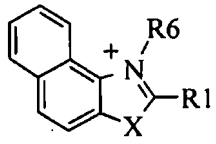
In another preferred embodiment, the pharmaceutical composition of the present invention comprises a compound of the formula Iq, wherein R1 is a radical of the formula (g), as depicted in formula It:



(It)

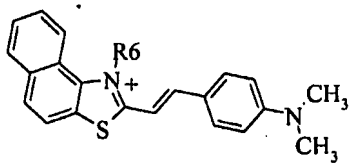
According to this embodiment, R10 may be ethyl, as exemplified by the novel compound herein designated **Compound 13** in the Appendix A just before the Claims.

In yet another embodiment of the present invention, the pharmaceutical composition comprises a compound of the general Formula I, wherein R4 and R5 are hydrogen, R2 and R3 together with the carbon atoms to which they are attached form a condensed benzene ring and R6 is C1-C6 alkyl, as depicted in formula Iu:



(Iu)

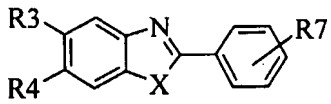
According to this embodiment, in the formula Iu, R1 may be a radical of the formula (i), as in the formula Iv:



(Iv)

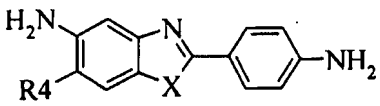
In the formula Iv, R6 is preferably methyl, as exemplified by the compound herein designated **Compound 14** in the Appendix A just before the Claims. This compound is described in the literature [CAS No. 6285-35-4] but no biological activity has been disclosed for the compound.

In another preferred embodiment of the present invention, the pharmaceutical composition comprises a compound of the general Formula I, wherein R1 is a radical (a), R2 and R5 are hydrogen, R6 is absent, and R3 and R4 independently are each hydrogen or -NR8R9 as depicted in formula Iw:



(Iw)

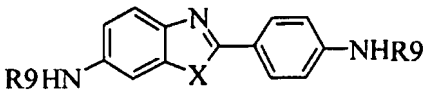
In a preferred embodiment, in the formula Iw, R7 is at the para position, and R3 and R7 are -NR8R9, wherein R8 and R9 are both hydrogen, as depicted in the formula Ix:



(Ix)

In one preferred embodiment, in the compound of formula Ix, X is –NH- and R4 is methyl, as exemplified by the compound herein designated **Compound 15 in** the Appendix A just before the Claims. This compound is described in the literature [CAS No. 70500-05-9] but no biological activity is disclosed for it.

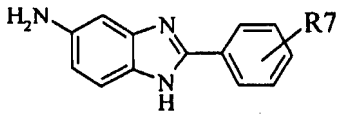
In still another preferred embodiment, in the compound of Formula Iw, R7 is at the para position, R3 is H, R4 and R7 are both -NHR9, as in formula Iy:



(Iy)

In a preferred embodiment, in the compound of Formula Iy, X may be S, and R9 may be benzoyl substituted at the para-position by $-NH_2$, as exemplified by the compound herein designated **Compound 16** in the Appendix A just before the Claims. This compound is described in the literature [CAS No. 330998-38-4] but no biological activity has been disclosed for the compound.

In yet another embodiment of the present invention, in the compound of formula Iw above, R4 is H and R3 is $-NH_2$, as depicted in formula Iz below:

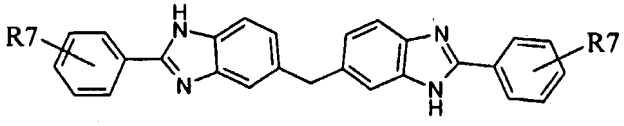


(Iz)

In one preferred embodiment, in formula Iz, R7 is benzimidazol-2-yl substituted by $-NH_2$ at position 5, as exemplified by the compound herein designated **Compound 17** in the Appendix A just before the Claims. This compound is described in the literature [Chauhan et al., (1986); CAS No. 28689-19-2] but no biological activity has been disclosed for the compound.

The present invention further relates to novel compounds of the general formula I and to pharmaceutically acceptable salts thereof.

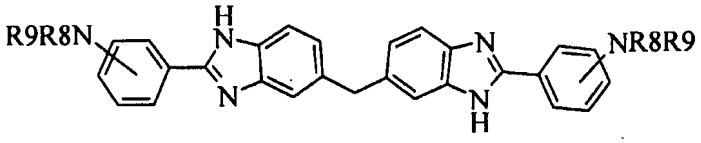
In one embodiment, the invention relates to a heterocyclic compound of the formula



(Ib)

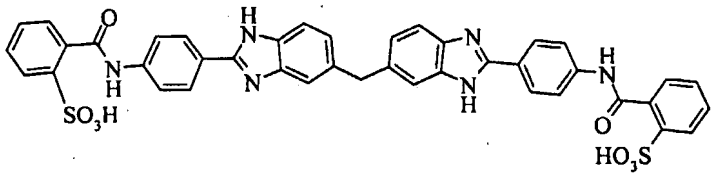
Ib:

wherein R7 is preferably –NR8R9 as depicted in formula Ic:

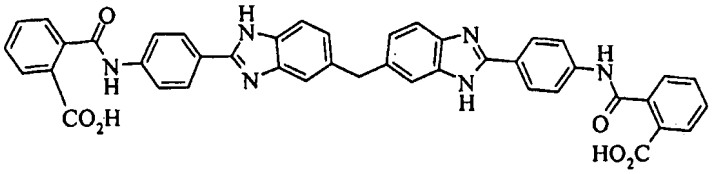


(Ic)

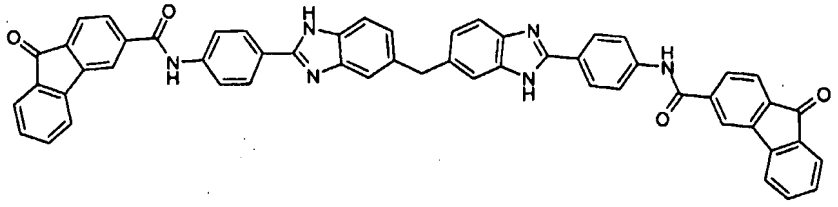
In a preferred embodiment, in the compound of formula Ic, the radicals –NR8R9 are at the para-positions of the phenyl rings, R8 is H and R9 is benzoyl substituted at the ortho-position by $-SO_3H$ or –COOH, or R9 is a 9-oxo-fluoren-3-oyl radical, as exemplified by the compounds herein designated **Compounds 2-4** of the formulas:



Compound 2

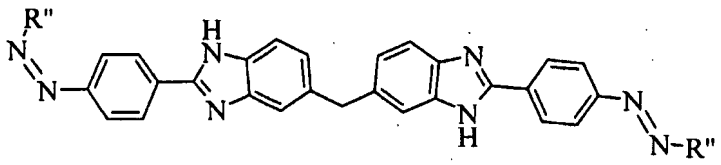


Compound 3



Compound 4

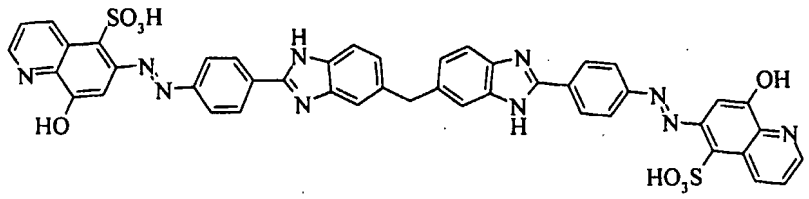
In a further embodiment, in the compound of formula Ib, R7 is –N=N-R" at the para position as depicted in the formula Id:



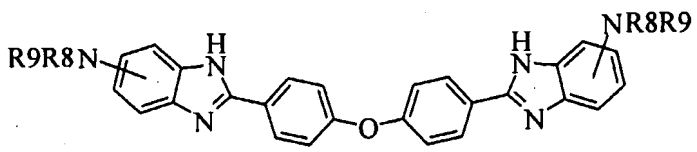
(Id)

wherein R" is heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S and being optionally substituted by -OH, -COOH and/or -SO_3H.

According to this embodiment, R" is preferably a quinoline residue substituted by both -OH and -SO_3H such as the 5-sulfo-8-hydroxyquinolin-7-yl group, as depicted in the compound herein designated **Compound 5** of the formula:

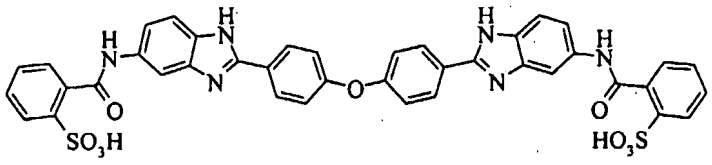


In yet another embodiment, the invention relates to a heterocyclic compound of the formula Ig:

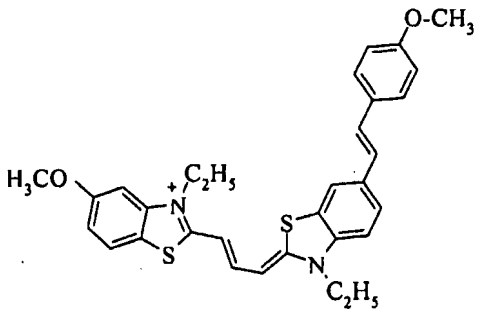


(Ig)

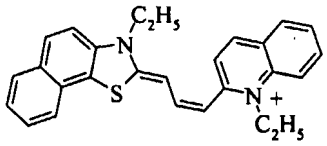
wherein the radicals –NR8R9 are at the 5-position of the imidazole rings, R8 is H and R9 is benzoyl substituted at the ortho-position by –SO_3H, as exemplified by the compound herein designated **Compound 7** of the formula:



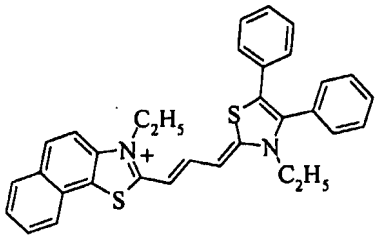
The invention further relates to the heterocyclic compounds herein designated **Compounds 10, 12** and **13** of the formulas:



Compound 10



Compound 12



Compound 13

The **Compounds 1-7, 10, 12** and **13** of the invention can be prepared as illustrated in **Schemes 1** to **11** in the Appendix B, herein. The synthesis involves initial construction of the benz-1,3-azole backbone followed, if desired, by functionalization of the terminal amino groups.

Thus, **Compound 1** was prepared in five steps from 4,4'-methylenedianiline according to **Scheme 1** (depicted in the Appendix B just before the Claims). The amino groups of 4,4'-methylenedianiline were protected by acetylation (step a), followed by nitration of the acetylated amino compound at the ortho positions with nitric acid (step b), deprotection of the amino groups with KOH (step c), reduction of the nitro groups to afford the tetra-amino compound (step d), and polyphosphoric acid mediated condensation of the tetra-amino compound with *p*-aminobenzoic acid to give **Compound 1** as a green powder. **Compounds 2, 3** and **4** were prepared from **Compound 1** by acylation of the amino groups with the appropriate cyclic anhydride or acyl chloride, as shown in **Schemes 2, 3** and **4**, respectively. **Compound 5** was synthesized as shown in **Scheme 5** by reaction of **Compound 1** with sodium nitrite followed by reaction of the bis-diazonium salt with 8-hydroxyquinoline-5-sulfonic acid.

Compound 6 was prepared according to **Scheme 6** in three steps. Polyphosphoric acid (PPA) mediated condensation of 4,4'-oxy-bis(benzoic acid) with 1,2-phenylenediamine gave 4,4'-oxy-bis(phenylbenzimidazole) (step a), which was nitrated at the benzimidazole rings in the presence of nitric acid (step b), and reduction of the nitro derivative (step c) gave the diamino **Compound 6** as the sole product. **Compound 6** was treated with sulfobenzoic anhydride according to **Scheme 7,** resulting in the bis-sulfobenzoylamino **Compound 7**.

Compound 10, 12 and **13** were prepared in multi-step syntheses from uncharged starting materials as shown in **Schemes 8-9, 10** and **11,** respectively. The synthesis of **Compound 10** began with the Wittig reaction of the phosphonium salt of 1-chloromethyl-4-methoxybenzene and 2-methylbenzothiazole-6-carbaldehyde as shown in **Schemes 8** and **9**.

Compound 12 was prepared in multiple steps from 2-methylnaphthol [2,1-d]thiazole, as shown in **Scheme 10**. **Compound 13** was prepared similarly to **Compound 12** from 2-methylnaphtho[2,1-d]thiazole and 2-methyl-4,5-diphenyl-thiazole, as shown in **Scheme 11**.

Although **Schemes 1-11** indicate exact structures, the methods apply widely to analogous compounds of Formula I, given appropriate consideration to protection and deprotection of reactive functional groups by methods standard to the art of Organic Chemistry. For example, in order to prevent unwanted side reactions, hydroxy groups generally need to be converted to ethers or esters during chemical reactions at other sites in the molecule. The hydroxy protecting group is readily removed to provide the free hydroxy group. Amino

groups and carboxylic acid groups are similarly derivatized to protect them against unwanted side reactions. Typical protecting groups, and methods for attaching and cleaving them, are described fully by Greene and Wuts in Protective Groups in Organic Synthesis, John Wiley and Sons, New-York (2nd Ed, 1991) and McOmie, Protective Groups in Organic Chemistry, Plenum Press, New-York, 1973.

For the preparation of other compounds of Formula I, similar procedures known to those of skill in the art may be used.

The inhibitory effect of the compounds of the present invention on heparanase activity can be evaluated by several methods carried out in vitro, ex vivo, or in vivo.

Some of the in vitro assays used according to the present invention were described in US 6,190,875. In these assays, heparanase is incubated with a heparanase substrate in the presence and in the absence of a compound of the present invention, and the inhibitory effect of the compound on the catalytic activity of the heparanase on its substrate is evaluated.

The heparanase may be natural mammalian heparanase, such as human heparanase purified as described in U.S. Patent 5,362,641 or, preferably, recombinant mammalian, e.g. human or mouse recombinant heparanase as described in US 5,968,822, US 6,190,875, and WO 99/57244, in purified or non-purified form. A source of non-purified recombinant heparanase is, for example, an extract of cells in which mammalian heparanase cDNA is expressed.

The heparanase substrate may be a natural heparan sulfate substrate, or an alternative substrate of the enzyme as described in U.S. 6,190,875, for example, heparin (e.g. heparin immobilized on a gel such as Sepharose), heparin fragments (e.g. several species of low molecular weight heparin), modified non-anticoagulant species of heparin, other sulfated polysaccharides (e.g. pentosan polysulfate), soluble HSPG or ECM.

Evaluation of the inhibitory effect can be carried out, for example, as described in US 6,190,875, by a size separation assay adapted for detection of degradation products of the heparanase substrate. Examples of such assays include gel electrophoresis and column chromatography.

Qualitative and quantitative evaluation of the catalytic activity of heparanase on its substrate and the inhibitory effect of a candidate inhibitor can be effected, for example, by colorimetric assays. Any colorimetric assay based on any color producing reaction is

envisaged by the invention, be it a simple color reaction, which is readily detectable, or a fluorimetric or a luminiscent (e.g., chemiluminiscent) reaction, which are readily detectable by fluorescence detecting techniques. Examples of such suitable colorimetric assays include, but are not limited to, the dimethylmethylene blue (DMB), tetrazolium blue and carbazole assays. Qualitative colorimetric assays include the dimethylmethylene blue (DMB) assay, which yields color shift in the presence of polyanionic compounds such as sulfated glycosaminoglycans having different sizes that are released from the substrate (soluble or immobilized), and the carbazole assay, which detects uronic acid derivatives present in complete hydrolyzates of products released from an immobilized substrate, both assays being applicable for crude extracts of heparanase and for the purified enzyme as well.

In a preferred embodiment, a quantitative evaluation is desired and the preferred in vitro assays are those which are adapted for detection of reducing moieties associated with degradation products of the heparanase substrate, preferably a reducing sugar assay. An example of a quantitative colorimetric assay is the tetrazolium blue assay which allows colorimetric detection of reducing moieties released from the substrate, e.g. heparan sulfate, which may be present either in soluble or immobilized form.

Another possibility, although less preferred, consists in evaluating the catalytic activity of heparanase on the substrate by radioactive techniques, in which case the substrate used is radiolabeled, either in vitro or metabolically.

The ex vivo assays for evaluating the inhibitory effect of the compounds on heparanase activity include angiogenic sprout formation and transmigration assays. The angiogenic sprout formation assay is carried out in the rat aorta model (Nicosia et al., 1997; Nicosia and Ottinetti, 1990), whereby rat aorta rings are embedded in a basement membrane-like matrix composed of ECM-derived proteins such as laminin and collagen type IV, and HSPG, thus constituting a relevant heparanase substrate. The rings then develop angiogenic sprouts and angiogenesis can be quantitated. The compounds to be tested are added to the embedded aortic rings and their effect on angiogenic sprout formation is then evaluated.

In the ex vivo transwell migration assay, immune cell migration is evaluated, optionally in the presence of a chemoattractant factor such as stromal cell-derived factor 1 (SDF-1), a process which mimics in vivo extravasation of immune cells from the vasculature to sites of inflammation. In this assay, immune cells such as lymphocytes are let to migrate

from the upper to the lower chamber through a transwell filter coated with a basement membrane-like matrix composed of ECM-derived proteins. The migration rate of the cells through the filter is then evaluated by counting the number of cells migrated through the filter (e.g. using a FACSort) compared to the number of cells added on top of the upper chamber. Over expression of heparanase in the immune cells results in an increase in the transmigration rate of the cells while addition of a heparanase inhibitor reduces the transmigration rate of the cells.

The inhibitory effect of the compounds on heparanase activity may be also assayed in vivo, for example, using the primary tumor growth or metastasis animal models or the sponge inflammation assay.

In the primary tumor animal model, animals are injected subcutaneously (s.c.) with tumor cells and treated with the heparanase inhibitors. Tumor growth is measured when animals in untreated control group start to die. For example, primary tumors may be generated with B16-F1 melanoma cells or with a highly metastatic subclone thereof injected s.c. into the flanks of mice. The mice are treated with heparanase inhibitors injected intraperitoneally (i.p.) twice a day starting 4 days after cell injection and are sacrificed and the tumor measured about 3 weeks after cell injection.

In the metastasis animal model, animals are injected intravenously (i.v.) with tumor cells and treated with the heparanase inhibitors. The number of lung metastasis is counted when animals in untreated control group start to die or about 3 weeks after cell injection. For example, metastasis may be generated with B16-F1 melanoma cells or with a highly metastatic subclone thereof injected i.v. to mice. The mice are treated with heparanase inhibitors injected i.p. at certain times following cell injection, and are then sacrificed and the number of lung metastasis is counted.

In the sponge inflammation assay, polyvinyl alcohol (PVA) sponges are implanted under the mouse skin and the mouse is kept untreated or is treated with a test inhibitor agent. One day later, the mouse is sacrificed, the sponges are taken out, squeezed into a tube and the number of cells in each sample is determined. After centrifugation, the myeloperoxidase (MPO) content may be determined in a suspension of cell pellets, and the TNF-α content in the supernatant of the sample. This assay mimics the inflammatory reaction resulting from the presence of a foreign body in the organism.

The heparanase inhibitors of the present invention can be used for the treatment of diseases and disorders caused by or associated with heparanase catalytic activity such as, but not limited to, cancer, inflammatory disorders and autoimmune diseases.

Thus, in one embodiment of the present invention, the compounds can be used for inhibition of angiogenesis, and are thus useful for the treatment of diseases and disorders associated with angiogenesis or neovascularization such as, but not limited to, tumor angiogenesis, ophthalmologic disorders such as diabetic retinopathy and macular degeneration, particularly age-related macular degeneration, reperfusion of gastric ulcer, and also for contraception or for inducing abortion at early stages of pregnancy.

In another embodiment of the invention, the compounds of general formula I are useful for treatment or inhibition of a malignant cell proliferative disease or disorder.

According to this embodiment and due to the angiogenesis inhibitory activity of the compounds, they can be used for the treatment or inhibition of non-solid cancers, e.g hematopoietic malignancies such as all types of leukemia, e.g. acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), myelodysplastic syndrome (MDS), mast cell leukemia, hairy cell leukemia, Hodgkin's disease, non-Hodgkin's lymphomas, Burkitt's lymphoma and multiple myeloma, as well as for the treatment or inhibition of solid tumors such as tumors in lip and oral cavity, pharynx, larynx, paranasal sinuses, major salivary glands, thyroid gland, esophagus, stomach, small intestine, colon, colorectum, anal canal, liver, gallbladder, extrahepatic bile ducts, ampulla of vater, exocrine pancreas, lung, pleural mesothelioma, bone, soft tissue sarcoma, carcinoma and malignant melanoma of the skin, breast, vulva, vagina, cervix uteri, corpus uteri, ovary, fallopian tube, gestational trophoblastic tumors, penis, prostate, testis, kidney, renal pelvis, ureter, urinary bladder, urethra, carcinoma of the eyelid, carcinoma of the conjunctiva, malignant melanoma of the conjunctiva, malignant melanoma of the uvea, retinoblastoma, carcinoma of the lacrimal gland, sarcoma of the orbit, brain, spinal cord, vascular system, hemangiosarcoma and Kaposi's sarcoma.

It is to be understood that the compounds of the general formula I are useful for treating or inhibiting tumors at all stages, namely tumor formation, primary tumors, tumor progression or tumor metastasis.

The compounds of general formula I are also useful for inhibiting or treating cell proliferative diseases or disorders such as psoriasis, hypertrophic scars, acne and sclerosis/scleroderma, and for inhibiting or treatment of other diseases or disorders such as polyps, multiple exostosis, hereditary exostosis, retrolental fibroplasia, hemangioma, and arteriovenous malformation.

In a further embodiment, the compounds of general formula I are useful for treatment of or amelioration of inflammatory symptoms in any disease, condition or disorder where immune and/or inflammation suppression is beneficial such as, but not limited to, treatment of or amelioration of inflammatory symptoms in the joints, musculoskeletal and connective tissue disorders, or of inflammatory symptoms associated with hypersensitivity, allergic reactions, asthma, atherosclerosis, otitis and other otorhinolaryngological diseases, dermatitis and other skin diseases, posterior and anterior uveitis, conjunctivitis, optic neuritis, scleritis and other immune and/or inflammatory ophthalmic diseases.

In another preferred embodiment, the compounds of general formula I are useful for treatment of or amelioration of an autoimmune disease such as, but not limited to, Eaton-Lambert syndrome, Goodpasture's syndrome, Grave's disease, Guillain-Barré syndrome, autoimmune hemolytic anemia (AIHA), hepatitis, insulin-dependent diabetes mellitus (IDDM), systemic lupus erythematosus (SLE), multiple sclerosis (MS), myasthenia gravis, plexus disorders e.g. acute brachial neuritis, polyglandular deficiency syndrome, primary biliary cirrhosis, rheumatoid arthritis, scleroderma, thrombocytopenia, thyroiditis e.g. Hashimoto's disease, Sjögren's syndrome, allergic purpura, psoriasis, mixed connective tissue disease, polymyositis, dermatomyositis, vasculitis, polyarteritis nodosa, polymyalgia rheumatica, Wegener's granulomatosis, Reiter's syndrome, Behçet's syndrome, ankylosing spondylitis, pemphigus, bullous pemphigoid, dermatitis herpetiformis, Crohn's disease and autism.

Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers or excipients. The carrier(s) must be acceptable in the sense that it is compatible with the other ingredients of the composition and are not deleterious to the recipient thereof.

The term "carrier" refers to a diluent, adjuvant, excipient, or any other suitable vehicle. Such pharmaceutical carriers can be sterile liquids such as water and oils.

The pharmaceutical composition can be administered systemically, for example by parenteral, *e.g.* intravenous , intraperitoneal or intramuscular injection. In another example, the pharmaceutical composition can be introduced to a site by any suitable route including intravenous, subcutaneous, transcutaneous, topical, intramuscular, intraarticular, subconjunctival, or mucosal, *e.g.* oral, intranasal, or intraocular.

In one specific embodiment, the pharmaceutical composition is administered to the area in need of treatment. This may be achieved by, for example, local infusion during surgery, topical application, direct injection into the inflamed joint, directly onto the eye, etc.

For oral administration, the pharmaceutical preparation may be in liquid form, for example, solutions, syrups or suspensions, or in solid form as tablets, capsules and the like. For administration by inhalation, the compositions are conveniently delivered in the form of drops or aerosol sprays. For administration by injection, the formulations may be presented in unit dosage form, *e.g.* in ampoules or in multidose containers with an added preservative.

The compositions of the invention can also be delivered in a vesicle, in particular in liposomes. In another embodiment, the compositions can be delivered in a controlled release system.

The amount of the therapeutic or pharmaceutical composition of the invention which is effective in the treatment of a particular disease, condition or disorder will depend on the nature of the disease, condition or disorder and can be determined by standard clinical techniques. In general, the dosage ranges from about 0.01 mg/kg to about 50-100 mg/kg. In addition, in vitro assays as well in vivo experiments may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease, condition or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems. For example, in order to obtain an effective mg/kg dose for humans based on data generated from mice or rat studies, the effective mg/kg dosage in mice or rats is divided by twelve or six, respectively.

The invention will now be illustrated by the following non-limiting examples.

EXAMPLES

For convenience and better understanding, the section of the Examples is divided into two subsections: (I) the Chemical Section describing the synthesis of the benz-1,3-azole compounds, and (II) the Biological Section describing the biological activity of the compounds.

I CHEMICAL SECTION

The **Compounds 1-17**, which formulas are presented in Appendix A hereinafter, are identified in the Examples by their numbers in bold. The methods of preparation of the compounds are depicted in Appendix B as **Schemes 1-11**. The intermediates are identified by the symbols ***i-xvii*** in bold-italics.

Materials

All reagents were purchased from Sigma-Aldrich Israel, Ltd., (Rehovot, Israel) and were used without further purification unless otherwise stated.

Compounds 8, 9, 11, 14, 15, 16, and **17** of the invention were purchased from ChemDiv, Chemical Diversity (San-Diego, CA, USA).

EXAMPLE 1. Synthesis of Compound 1.

Compound 1 was synthesized in five steps from 4,4'-methylenedianiline according to **Scheme 1**, as follows:

(a) Acetic anhydride (Ac_2O, 26 mL, 0.23 mol) was added dropwise to a clear solution of 4,4'-methylenedianiline (20.0 g, 0.1 mol) in acetic acid (75 mL) at 60°C. The reaction mixture was warmed to 90°C for 1 hour and then was allowed to cool to room temperature. The precipitate was filtered off and washed with water, thus obtaining the diacetylated ***intermediate i*** (28.1 g, 99% yield).

(b) A solution of ***intermediate i*** (28.1 g, 0.1 mol), obtained in the previous step, in acetic anhydride (250 mL) was cooled to 10°C at which point nitric acid (36 mL) was added dropwise. The mixture was allowed to react at 10°C for 1 hour and then was allowed to warm to room temperature. The mixture was poured onto ice water and a yellow precipitate appeared. The solid was filtered off and washed with water obtaining the nitrated ***intermediate ii*** as a light yellow solid (35.8 g, 97% yield).

(c) A methanolic solution of potassium hydroxide (15.29 g KOH, 0.27 mol in 54 mL methanol) was added dropwise to a solution of ***intermediate ii*** (35.8 g, 0.098 mol), in methanol (240mL). The reaction mixture was stirred for 3 hours at room temperature before it was poured onto water (450 mL). The precipitate that formed was filtered off to give a light orange solid identified as the nitrated diamino ***intermediate iii***. Recrystallization from ethanol gave a pure product (19.1 g, 67.7% yield).

(d) A stirred solution of the ***intermediate iii*** (17.4 g, 0.05 mol) and $SnCl_2 \cdot H_2O$ (90 g, 0.4 mol) in 32% HCl (200 mL) was maintained at 65-70°C for 4 hours. Then the solution was cooled to –20 °C and maintained at that temperature for 12 hours. As the solution was made basic to pH 9, a yellow precipitate appeared. The precipitate was filtered off and washed with water. The yellow solid was suspended in methanol (50 mL) and refluxed for 1 hour. After cooling to room temperature, the precipitate was collected and washed with water, thus obtaining ***intermediate iv***, 4,4'-methylenebis(o-diaminobenzene) (9.8 g, 71% yield).

^{1}H NMR (DMSO-d_6): δ= 6.38 (d, J = 7.7 Hz, 2H), 6.29(s, 2H), 6.19(d, J = 7.6 Hz, 2H), 4.28(s, 2H), 4.17(s, 2H), 3.42(s, 2H).

(e) Poly-phosphoric acid (PPA, 150 mL) was added to a mixture of the ***intermediate iv*** (5.01g, 21.97 mmol) and 4-aminobenzoic acid (6.01 g, 43.87 mmol). The reaction mixture was heated at 130°C for 3 hours and then was allowed to cool to room temperature. The reaction mixture was poured onto ice water (500 g) and made basic with NaOH (120 g, 3 mol), thus obtaining a green precipitate. The precipitate was filtered off, washed with water and dried to give **Compound 1** (6.5 gr, 69% yield).

^{1}H NMR (DMSO-d_6): δ= 7.82 (d, J = 8.0 Hz, 4H), 7.38 (d, J = 8.0 Hz, 2H), 7.33 (bs, 2H), 7.03(d, J = 8.1 Hz, 2H), 6.44 (d, J = 8.3Hz, 4H), 4.12 (bs, 2H).

EXAMPLE 2. Synthesis of Compound 2 and its sodium salt.

Compound 2 was prepared from **Compound 1** according to **Scheme 2**, as follows:

Compound 1 (4.67 g, 10.86 mmol), N,N'-dimethylacetamide (150 mL) and N-methyl-morpholine (15 mL) were added to a dry reaction flask maintained under dry conditions ($CaCl_2$). The reaction mixture was cooled to 0°C in an ice bath while sulfobenzoic acid cyclic anhydride (9.35 g, 21.74 mmol) was added, thus obtaining a clear solution. The

reaction mixture was left to react overnight at room temperature. Next, the solvent was removed under reduced pressure and the resulting mass was suspended in water (20 mL) at 60°C for 15 minutes. The precipitate that resulted was filtered off and washed with water, thus obtaining **Compound 2** (7.1 g, 82% yield).

^{1}H NMR (DMSO-d_6): δ= 11.74(s, 2H), 8.16 (d, J = 10.8Hz, 4H), 7.97(d, J = 10.8Hz, 6H), 7.91(d, J = 9.4 Hz, 2H), 7.73 (d, J = 10.1 Hz, 6H). 7.56-7.52(m, 4H), 7.47(d, J = 10.5 Hz, 2H),4.21(s, 2H).

Compound 2 (100 mg, 0.125 mmol), as prepared above, was dissolved in NaOH (100 mM, 50 mL) to a clear aqueous solution. Next, the basic solution was triturated with a dilute HCl solution (100 mM, 47.5 mL) in order to neutralize excess NaOH. The water was then evaporated to give a light-yellow solid salt mixture containing NaCl and the disodium salt of **Compound 2**.

EXAMPLE 3. Synthesis of Compound 3 and its triethylammonium salt.

Compound 3 was synthesized from **Compound 1** as depicted in **Scheme 3**, as follows:

Triethylamine (0.1 mL) and phthalicanhydride (14 mg, 0.09 mmol) were added to a solution of **Compound 1** (10 mg, 0.02 mmol) in dry pyridine (2 mL). The reaction mixture was left to react at room temperature under dry conditions overnight. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica gel, CH_2Cl_2: MeOH, 3:1 and Et_3N 0.5%), thus obtaining pure **Compound 3** as its triethylammonium salt (13 mg, 93% yield). The free acid may be obtained by slow addition of dilute HCl solution to an aqueous solution of the salt.

^{1}H NMR (DMSO-d_6): δ= 12.40 (bs, 2H), 8.08 (d, J = 5.8 Hz, 4H), 7.84(d, J = 5.8 Hz, 8H), 7.75(d, J = 5.8 Hz, 2H), 7.49(m, 8H), 6.63(m, 2H), 4.16 (s, 2H).

EXAMPLE 4. Synthesis of Compound 4.

Compound 4 was prepared from **Compound 1** according to **Scheme 4**, as follows:

A mixture of N-methylmorpholine (0.1 mL) and dimethylformamide (DMF, 92 mL) was added to a solution of **Compound 1** (13 mg, 0.03 mmol) in dry pyridine (1 mL) and methylene chloride (2 mL). Next, 9-fluorenone-3-carbonyl chloride (14 mg, 0.06 mmol) was

added and the slurry was left to react under dry conditions for 3 days at room temperature. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica gel, CH_2Cl_2: MeOH, 8:2), thus obtaining pure **Compound 4** (13 mg., 54% yield).

^{1}H NMR (DMSO-d_6): δ= 8.31 (d, J = 7.5 Hz, 4H), 7.71(m, 8H), 7.53(m, 6H), 7.30(m, 6H), 6.93(d, J = 8.1 Hz, 2H), 6.55(d, J = 8.4 Hz, 2H), 4.02 (s, 2H).

EXAMPLE 5. Synthesis of Compound 5.

Compound 5 was synthesized from **Compound 1** according to **Scheme 5**, as follows:

To slurry of **Compound 1** (86 mg, 0.2 mmol) in water (10 mL) a 32% solution of HCl (10 mL) was added. The reaction mixture was warmed to 50°C for 20 min obtaining a clear solution and then was cooled to 0°C and an additional portion of 32% HCl (10 mL) was added. A solution of sodium nitrite (35 mg, 0.5 mmol) in water (2 mL) was added to the cooled solution and the mixture was stirred for 30 minutes at 0°C, thus obtaining a yellow suspension of the diazonium salt. A separate solution made of 8-hydroxyquinoline-5-sulfonic acid (115 mg, 0.51 mmol) in water (20 mL) was treated with a solution of sodium hydroxide (40 mg, 1 mmol) in water (1 mL) followed by sodium carbonate (82 mg, 0.77 mmol). This solution was cooled to 0°C and the diazonium salt was added. The reaction mixture was left to react at 0°C for 5 hours and than was warmed to room temperature, at which point precipitation appeared. The product was filtered off, washed with sodium acetate solution and dried, obtaining **Compound 5** as a dark brown powder in 30% yield. TLC showed a single spot at R_f=0.45 (silica RP-18, BuOH (3.5):Pyridine (2):Ammonia (3):H_20 (1.5)).

EXAMPLE 6. Synthesis of Compound 6.

Compound 6 was synthesized from 4,4'-oxybis(benzoic acid) in 3 steps, according to **Scheme 6**, as follows:

(a) A mixture of 4,4'-oxybis(benzoic acid) (5 g, 19.38 mmol) and 1,2-phenylenediamine (2 equivalents) in poly-phosphoric acid (PPA, 300 mL) was heated at 130°C for 5 hours. The reaction solution was poured hot into ice water (300 mL) and the solution was made basic by the addition of a 10% NaOH solution (2 X 100 mL). The

precipitate that formed was filtered off and washed with a 10 mM solution of NaOH (20 mL), thus obtaining the desired ***intermediate v*** (7.73 g) in the form of a light gray powder. This product was used in the next step without further purification.

^{1}H NMR (DMSO-d_6): δ= 8.23 (d, J = 10.5 Hz, 4H), 7.59 (bs, 4H), 7.27 (d, J = 10.0 Hz, 4H), 7.19 (dd, J_1 = 4.0 Hz, J_2 = 3.5 Hz, 4H).

(b) The ***intermediate v*** obtained in the previous step (5 g, 12.44 mmol) was added to a solution of HNO_3 (300 mL) maintained on ice and the mixture was slowly allowed to warm to room temperature. The solution was next poured into 100 g ice initiating the precipitation of the dinitro ***intermediate vi***. The precipitate was filtered off and the solvent was removed under reduced pressure, obtaining further amount of the crude ***intermediate vi***. This product was used in the next step without further purification.

(c) A suspension of the crude ***intermediate vi*** obtained in the previous step and stannous chloride dihydrate (7.666 g, 40 mmol) in 35% aqueous HCl (20 mL) was heated at 100 °C for 4 hours. The reaction mixture was cooled to room temperature and basified with 20% NaOH. Extraction with $CHCl_3$ followed by solvent evaporation under reduced pressure, afforded the crude product. Recrystallization from ethyl acetate gave **Compound 6** in the pure form.

^{1}H NMR (DMSO-d_6): δ= 8.07 (d, J = 8.6 Hz, 4H), 7.23(d, J = 8.5 Hz, 1H), 7.16(d, J = 8.5 Hz, 4H), 6.65 (s, 1H), 6.50(d, J = 8.4 Hz, 1H).

EXAMPLE 7. Synthesis of Compound 7 and its ammonium salt.

Compound 7 was synthesized from **Compound 6** according to **Scheme 7**, as follows:

Sulfobenzoic anhydride (18.0 mg, 4.3 eq) and Et_3N (0.5 mL) were added to a solution of **Compound 6** (10.0 mg, 0.023 mmol), obtained pure as described in Example 5 above, in dry pyridine (2 mL). The reaction mixture was allowed to react at room temperature for 3 days. The solvent was removed under reduced pressure to obtain crude **Compound 7**. Purification by flash chromatography (silica gel, Methanol- EtOAc 3:2) gave the pure **Compound 7** (20 mg, 90% yield).

^{1}H NMR (DMSO-d_6): δ= 11.61 (s, 2H), 8.40 (s, 2H), 8.27 (d, J = 8.6 Hz, 4H), 7.92 (bs, 2H), 7.77(d, J = 8.8 Hz, 2H), 7.54-7.47(m, 12H).

To a solution of **Compound 7** (200 mg, 0.30 mmol) dissolved in methanol was added a solution of ammonium hydroxide (20 mmol). The resulting solution was stirred and the excess ammonia and water were evaporated under reduced pressure to dryness. Thus the diammonium salt of **Compound 7** was obtained as a light yellow powder.

EXAMPLE 8. Synthesis of Compound 10

Compound 10 was prepared in a multi-step synthesis as shown in **Schemes 8** and **9**, as follows:

A solution of triphenylphosphine (3.5 g, 13.4 mmol) in dry benzene (60mL) was stirred at -10°C for 1 hour. To the cold solution there was added drop-wise a solution of 1-chloromethyl-4-methoxybenzene (2.0 g, 12.8 mmol) in dry benzene (10 mL). The reaction mixture was allowed to warm to room temperature and was allowed to stir overnight. Then the solids were filtered off and washed with warm benzene. The solvent was removed under reduce pressure obtaining the corresponding triphenylphosphonium salt. The crude salt was added without further purification to a cold clear solution of sodium hydride (50%, 6.5 g, 13.5 mmol) in dry chlorobenzene (50 mL) and the reaction mixture was warmed to 50°C and stirred for 1 hour. To this mixture 2-methyl-benzothiazole-6-carbaldehyde (2.4 g, 13.6mmol) was added in one portion and the reaction mixture was left to react for 6 additional hours before it was cooled to room temperature. The solution was filtered off and the solvent was removed under reduce pressure obtaining the ***intermediate vii***.

To a solution of ***intermediate vii*** (200 mg, 1.01 mmol) in chlorobenzene there was added Ethyl-4-chlorobenzensulfonate (350 mg, 1.59 mmol). The reaction mixture was refluxed for 6 hour, allowed to cool to room temperature, thus obtaining ***intermediate viii***.

The crude ***intermediate viii*** was refluxed in concentrated HCl (32%, 50 mL) for 2 hour. The reaction mixture was allowed to cool to room temperature and the crude ***intermediate ix*** was filtered.

To 5-methoxy-2-methylbenzothiazole (200 mg, 1.01 mmol) in chlorobenzene were added Ethyl-4-chlorobenzensulfonate (350 mg, 1.59 mmol) in one portion. The reaction mixture was refluxed for 6 hour then was allowed to cool to room temperature, thus obtaining ***intermediate x***. The crude ***intermediate x*** was dissolved in toluene (100mL) obtaining dark slurry. The reaction mixture was warmed to 50°C and a solution of N,N'-

diphenylformamidine (355 mg, 1.81 mmol) in acetic anhydride (50 mL) was added in one portion. The reaction mixture was allowed to react at 50°C over night. The crude product was filtered and dried in a reduced pressure oven obtaining ***intermediate xi***.

A mixture of the ***intermediates xi*** and ***ix*** in acetic anhydride (150 mL) were added sodium acetate (200 mg, 2.44 mmol) and potassium iodide (200 mg, 1.2 mmol) and the reaction mixture was stirred at 50°C for 12 hours. The reaction mixture was filtered and the **Compound 10** was obtained.

Example 9. Synthesis of Compound 12

Compound 12 was prepared in a multi-step synthesis as shown in **Scheme 10**, as follows:

To a solution of 2-Methyl-naphthol [2,1-d]thiazole (200 mg, 1.01 mmol) in chlorobenzene were added Ethyl-4-chlorobenzensulfonate (350 mg, 1.59 mmol). The reaction mixture was refluxed for 6 hours before the solution was cooled down to room temperature and ***intermediate xii*** was collected.

The crude ***intermediate xii*** was refluxed in concentrated HCl (32%, 50mL) for 2 hours. The reaction mixture was allowed to cool to room temperature and ***intermediate xiii*** was filtered.

A black slurry of 1-ethyl-2-methylquinolinum iodide (520mg, 1.74mmol) in toluene (100mL) was treated at 50°C with N,N'-diphenylformamidine (355 mg, 1.81 mmol) in acetic anhydride (50mL). The reaction mixture was allowed to react at 50°C over night. The crude product was filtered and dried in a reduce pressure oven obtaining acetic acid 3-(1-ethyl-quinolin-2-yl)-1-phenyl-allyl ester iodide salt ***intermediate xiv***.

To a reaction mixture of the ***intermediates xiv*** and ***xiii*** in acetic anhydride (150mL) were added sodium acetate (200mg, 2.44mml) and potassium iodide (200mg, 1.2mmol). The reaction mixture was stirred at 50°C for 12 hours. The reaction mixture was filtered, thus obtaining **Compound 12**.

^{1}H-NMR (DMSO-*d*6) ppm: 8.31 (bm, 3H), 8.11 (m, 3H), 7.95-7.65 (bm, 5H), 7.55 (t,1H), 7.45 (t, 1H), 6.7 (d, 1H), 6.5 (d, 1H), 4.52 (m, 4H), 1.4(m, 6H).

Example 10. Synthesis of Compound 13

Compound 13 was prepared from 2-methylnaphtho[2,1-d]thiazole and 2-methyl-4,5-diphenyl thiazole following the procedure described for **Compound 12**, as shown in **Scheme 11**.

II BIOLOGICAL SECTION

Materials

Heparin Sepharose CL-6B was purchased from Pharmacia (Amersham Pharmacia Biotech) Uppsala, Sweden ; 1,9-Dimethylmethylene blue (DMB), tetrazolium blue and heparan sulfate were purchased from Sigma-Aldrich (Rehovot, Israel); MCDB 131 medium was purchased from Clonetics (San Diego, CA, USA); DMEM and fetal calf serum were purchased from Gibco BRL (InVitrogen Corporation, CA, USA) ; glutamine and gentamicin were purchased from Biological Industries (Bet Haemek, Israel). Matrigel was kindly provided by Dr. H. Kleinmann, NIDR, NIH, Bethesda, MD, USA.

Methods

(a) In vitro Dimethylmethylene blue (DMB) assay for heparanase activity

Heparin Sepharose CL-6B beads were added up to the top of the wells of a multiscreen column loader (Millipore). A 96-well multiscreen plate containing 0.65 μm hydrophilic, low protein binding, Durapore membrane (Millipore) was placed, upside down, on top of the multiscreen column loader. The column loader and the multiscreen plate were held together, turned over, and the beads were uniformly transferred from the column loader to the multiscreen plate. Double-distilled water (DDW) was then added to the beads, which were allowed to swell for one minute, and then washed (three times) with DDW under vacuum. Heparin concentration was estimated to be 20 μM/well.

Human recombinant heparanase of at least 50% purity was obtained by expression in the CHO cells S1-11 subclone (generated as described for CHO clones S1PPT-4 and S1PPT-8 in WO 99/57244). Active human recombinant heparanase, purified from the CHO cell extracts by ion exchange chromatography (as described for the CHO 2TT1-8 subclone in WO 99/57244), was added (5 ng/well) to a reaction mixture containing 20 mM phosphate

citrate buffer, pH 5.4, 1 mM $CaCl_2$, 1 mM NaCl, and 1 mM dithiothreitol (DTT; total volume of 100 µl). After 3-hour incubation at 37° C in a incubator on a vortex shaker, the heparanase reaction products were filtered under vacuum and collected into a 96-well polystyrene flat bottom plate (Greiner Cat. No. 655101). To each well, phosphate-buffered saline (PBS) containing 1% bovine serum albumin (BSA; 75 µl/well) and DMB (32 mg of DMB were dissolved in 5 ml ethanol, diluted to 1 liter with formate buffer containing 4 g sodium formate and 4 ml formic acid; 125 µl /well) were added. Color was developed after 5 minutes, and the absorbance of the samples was determined using a spectrophotometer (CECIL CE2040) at 530 nm. The absorbance correlated to heparanase activity. As a control, heparanase was added to the heparin Sepharose swollen beads in the multiscreen plate and the heparanase reaction products were filtered immediately thereafter and the absorbance of these control samples was subtracted from all other samples.

Alternatively, instead of the partially purified human recombinant heparanase enzyme as above, crude extracts of CHO cells S1-11 subclone expressing human recombinant or crude extracts of CHO cells mhG9 clone expressing mouse recombinant heparanase (generated with the mouse heparanase cDNA as described for CHO clones expressing human recombinant heparanase in WO 99/57244) were used. The cell extracts were centrifuged and resuspended in 20 mM phosphate citrate buffer, pH 5.4 containing 50 mM NaCl. The cells were lysed by three cycles of freezing and thawing. The cell lysates were centrifuged (10000xg for 5 min), supernatants were collected and then assayed for heparanase activity using the DMB assay.

In order to examine whether a test compound exhibits an inhibitory effect on the heparanase activity, each compound was dissolved in dimethylsulfoxide (DMSO) and added, at a concentration range of 1-30 µM, to the heparin Sepharose swollen beads in the 96-multiscreen plate. The partially purified human recombinant heparanase or the crude cell extracts expressing either human or mouse recombinant heparanase was added for a 3-hour incubation and the reaction continued as described above. Color was developed and the absorbance was measured as described above. The IC_{50} value (the concentration at which the heparanase activity was inhibited by 50%) for each compound was evaluated.

(b) In vitro tetrazolium blue assay for heparanase activity

Human recombinant heparanase of at least 50% purity (obtained by expression in the CHO cells S1-11 subclone as described in (a) above) was added (4 ng) to each well of a 96-well microplate and incubated in a reaction mixture containing 20 mM phosphate citrate buffer, pH 5.4, 1 mM $CaCl_2$, 1 mM NaCl, and 4 μM heparan sulfate (final volume of 100 μl). After 3 hours of incubation at 37° C in an incubator on a vortex shaker, the reaction was stopped by the addition of tetrazolium blue reagent (0.11% tetrazolium blue in 0.1 M NaOH; 100 μl/well). Color was developed by incubation of the plates at 60°C for 2 hours. For each assay, a control reaction, which did not contain the substrate (heparan sulfate), was included. Color intensity was quantitatively determined in a microplate reader (Dynatech) at 580 nm. Heparanase activity was calculated as the difference between the O.D of the sample containing the substrate, and the O.D. of the sample not containing the substrate. The background O.D. produced by the substrate was also subtracted from all the samples. The absorbance correlated to heparanase activity. The IC_{50} value (the concentration at which the heparanase activity was inhibited by 50%) for each compound was evaluated.

(c) Ex vivo angiogenic sprout formation assay for heparanase activity

As described in the Background section, previous studies have demonstrated the involvement of heparanase in angiogenesis. In order to test whether the heparanase inhibitors of the present invention can inhibit angiogenesis, the rat aorta model of angiogenesis as previously described (Nicosia et al., 1997; Nicosia and Ottinetti, 1990) was used with some modifications. In this model, the rat aortic endothelium exposed to a three-dimensional matrix of collagen or other ECM-derived proteins, switches to a microvascular phenotype, generating branching networks of microvessels. Angiogenesis is triggered by the injury caused by the dissection procedure and does not require stimulation by exogenous growth factors. Therefore, the rat aorta model can be used to investigate the endogenous mechanisms by which blood vessels regulate angiogenesis during wound healing.

Briefly, thoracic aortas were excised from 2- to 3-month-old Fischer 344 male rats, rinsed in serum-free MCDB 131 growth medium containing 50 μg/ml gentamicin, cleaned of periadventitial fibroadipose tissue, and cross-sectioned at ~1 mm intervals. Freshly cut aortic rings were rinsed in serum-free MCDB 131 medium and each ring was embedded in Matrigel

(a basement membrane-like matrix composed of ECM-derived proteins such as laminin and collagen type IV and others, and HSPG, thus constituting a relevant heparanase substrate). Matrigel cultures were transferred to 18-mm wells of 4-well plates (Nunc) and grown at 35.5°C in 0.5 ml of serum-free MCDB131 medium that was changed 3 times a week. Angiogenesis was quantitated by counting the number of neovessels according to published criteria (Nicosia and Ottinetti, 1990). In order to examine the inhibitory effect, a test compound was added to the Matrigel aortic ring cultures and its effect on reduction of the number of new microvessels was determined in comparison with untreated cultures.

(d) <u>In vivo mouse melanoma primary tumor growth assay for heparanase activity</u>

Instead of using a primary tumor cell line, primary tumor was generated in C57BL mice by cells herein designated FOR cells, which were generated as follows: B16-F1 mouse melanoma cells (ATCC No. 6326) were grown in DMEM containing 10% fetal calf serum, 2 mM glutamine, and 50 μg/ml gentamicin. A subclone of the B16-F1 cell line, F1-J, produced large amounts of melanin and exhibited a highly metastasis potential. These highly metastatic F1-J cells were injected to syngeneic mice (100,000 cells, s.c.). Cells from metastases that were formed were cultured in different conditions. A clone, F1-LG, designated herein FOR, was selected by its high heparanase expression and activity using the reverse transcriptase-polymerase chain reaction (RT-PCR) and the radiolabeled ECM degradation analyses, respectively, as previously described (Vlodavsky et al., 1999; U.S. 6,190,875).

FOR cells were grown in DMEM containing 10% fetal calf serum, 2 mM glutamine, and 50 μg/ml gentamicin until they reached confluence (typically 4-5 days) and then splitted (1:5). This splitting yielded subconfluent and growing cells at day 7, the day of cell injection, at which the cells were trypsinized, washed with PBS and counted to yield a cell suspension of 10^6 cells/ml in PBS. Male C57BL mice (~20 gram each; at least 10 mice/group) were injected s.c. on the flank with a suspension of the FOR cells (100 μl/mouse). Four days later, a test compound dissolved in DMSO was injected (100 μl) i.p to the mice, twice a day (morning and evening). Each compound was injected at either 1 or 2 different concentrations (0.1 and/or 0.5 mg/mouse/day). Control mice were injected i.p. with DMSO only (100 μl). Mice were observed daily, and usually three weeks after cell injection, mice were sacrificed, the tumors were harvested and weighted.

(e) In vivo mouse melanoma metastasis assay for heparanase activity

FOR cells were cultured as described in (d) above. After trypsinization, the cells were washed with PBS and counted to yield a cell suspension of $1.5x10^6$ cells/ml in PBS. Male C57BL mice (~20 gram each; at least 10 mice/group) were injected i.v. with a suspension of the FOR cells (100 µl/mouse). A test compound dissolved in DMSO was injected (100 µl) i.p to the mice 4 and 8 hours after cell injection. The compound was injected at 1 or 2 different concentrations (0.5 and/or 1 mg/mouse/day). Control mice were injected i.p. with DMSO only. Mice were observed daily, and three weeks after cell injecion, mice were sacrificed, the lungs were fixed in Bouen's solution and scored for the number of metastatic nodules as previously described (Vlodavsky et al., 1995).

(f) Transmigration assay for heparanase activity

An in vitro chamber-like transmigration system was established by using transwell filters coated with a reconstituted basement membrane-like matrix (Matrigel). Matrigel is was composed of laminin, collagen type IV, entactin and nidogen, as well as of HSPG, thus constituting a relevant heparanase substrate. The cells used in the experiment were mock-transfected Eb murine lymphoma cells not expressing heparanase and stable *hpa*-transfected Eb murine lymphoma cells overexpressing heparanase (both cells described by Vlodavsky et al., 1999), and the migration rate of the cells trough Matrigel was evaluated first in the absence and in the presence of the chemoattractant SDF-1. Once the transmigration of the cells to the lower chamber was shown to be well correlated with the heparanase expression levels and activity, the transmigration of the Eb cells overexpressing heparanase was tested after treatment with the heparanase inhibitors of the invention. Addition of the heparanase inhibitor reduces the transmigration rate of the cells.

Example II (1). In vitro inhibition of heparanase activity by compounds of the invention

The inhibition of heparanase activity by the compounds of the present invention was first detected in two colorimetric in vitro assays, i.e., the DMB assay and the tetrazolium blue assay as described in Methods (a) and (b) above. The human recombinant heparanase (designated h-hepa) expressed in CHO cells S1-11 subclone was used herein either in its partially purified form (50% purity) or in crude cell extracts, and the mouse recombinant heparanase (designated m-hepa) expressed in CHO cells mhG9 clone was used herein in crude cell extracts only.

The results of the IC_{50} values of the different compounds are shown in Table 1. All the tested compounds were found to inhibit heparanase activity at micromolar concentrations. However, three of them, namely **Compounds 2, 9** and **12,** were shown to be highly potent (IC_{50} values in the range of 1.5 to 3.3 μM in the DMB (h-hepa) assay compared to IC_{50} values in the range of 4.3 to 36 μM of the other compounds).

Table 1. IC_{50} values of the tested compounds for inhibition of heparanase as detected by the in vitro DMB and tetrazolium assays.

Compound	DMB (h-hepa)	Tetrazolium (h-hepa)	DMB of cell extract (h-hepa)	DMB of cell extract (m-hepa)
1	5	10	6.4	9
2	1.5	2.7	7	4
3	4.8	8	n.d.	67
4	4.1	n.d.	n.d.	n.d.
5	19	n.d.	n.d.	n.d.
6	6.7	18	7	6
7	4.3	4.5	13	16
8	8.9	n.d.	13	12
9	2.3	3.1	4	6
10	6	n.d.	7	5
11	6	n.d.	4	6
12	3.3	7	6	6
13	4.8	n.d.	19	14
15	36			
16	6.4	12.9	7	6
17	10	n.d.	n.d.	n.d.

Example II (2). Inhibition of angiogenesis by Compounds 1 and 6

The angiogenesis inhibitory effect of **Compound 1** and **Compound 6** was assayed using the angiogenic sprout formation assay described in Method (c) above. The results are presented in Table 2.

Table 2. Effect of Compounds 1 and 6 on angiogenic sprout formation

Compound	120μM	12μM	1.2μM	0.12μM	Control
1	---	+/-	+/-	+	+++
6	---	n.d.	n.d.	n.d.	+++

As shown in Table 2, embedding of rat aorta rings in Matrigel in the absence of any inhibitor (control) yielded extensive angiogenic sprouting (marked by +++). Addition of active heparanase to the rat aorta rings accelerated the angiogenic sprout formation (not shown) implying a major role of heparanase in this process. Treatment of the aorta rings with **Compound 1** was found to reduce angiogenic sprout formation at a concentration of 0.12 μM and to completely inhibit it at a concentration of 120 μM (marked by ---). Treatment with **Compound 6** at a concentration of 120 μM completely inhibited sprout formation (---).

Example II (3). Inhibition of mouse melanoma primary tumor growth by Compounds 1 and 6 and of metastasis by Compound 6

Since **Compounds 1 and 6** of the present invention were shown in Example II (2) herein to inhibit angiogenic sprout formation, and since tumor progression is angiogenic-dependent, the effect of these compounds on primary tumor growth was assayed as described in Method (d) above. The results are summarized in Tables 3 and 4 for **Compounds 1** and **6**, respectively.

As shown in Tables 3 and 4, untreated control mice developed primary tumors with an average weight of 0.1 to 0.2 g. Treatment with **Compound 1** (0.5 mg/mouse/day) totally abolished the tumor (Table 3), and treatment with **Compound 6** at the same dose significantly reduced tumor weight to an average of 0.01 g (Table 4).

The effect of **Compound 6** was further tested in melanoma metastasis as described in Method (e) above. The results, summarized in Table 5, show that the average number of metastatic nodules in the lungs of control, untreated mice was 23, while treatment with increasing doses of **Compound 6** (from 0.5 to 1.0 mg/mouse/day) significantly reduced the number of lung metastatic nodules (5 nodules in mice injected with 1 mg/mouse/day).

Table 3. Effect of Compound 1 on mouse melanoma primary tumor growth

Dose [mg/mouse/day] Tumor weight (gr)	**Control**	**0.1**	**0.5**
	0.16	0.23	0
	0.13	0.04	0
	0.27	0.18	0
	0.12	0	0
	0.28	0.02	0
	0.19	0.23	0
	0.08	0.7	0
	0.29	0	0
	0.21	0.05	0
Median	0.19	0.05	0
Range	0.08-0.29	0-0.23	0

Table 4. Effect of Compound 6 on mouse melanoma primary tumor growth

Dose [mg/mouse/day] Tumor weight (gr)	Control	0.5
	0.18	0.15
	0.34	0.03
	0.78	0.02
	0.1	0.01
	0.07	0
	1.04	0
	0.09	0
	0.01	
	0	
Median	0.1	0.01
Range	0-1.04	0-0.15

Table 5. Effect of Compound 6 on mouse melanoma metastasis

Dose [mg/mouse/day] Number of metastasis	**Control**	**0.5**	**1.0**
	30	29	1
	5	7	5
	57	6	17
	21	30	26
	37	5	5
	23	4	4
	20	1	1
	22	6	6
	85	4	4
Median	23	6	5
Range	5-85	1-30	1-26

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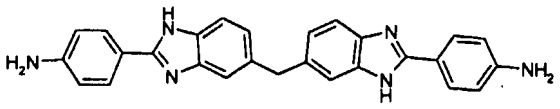
5

APPENDIX A- Structures of Compounds 1-17

Compound 1



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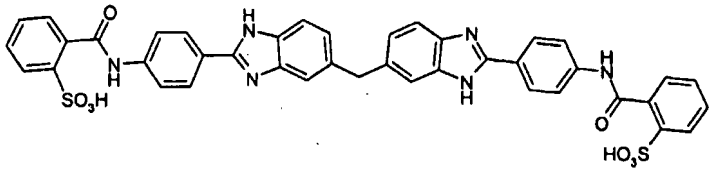

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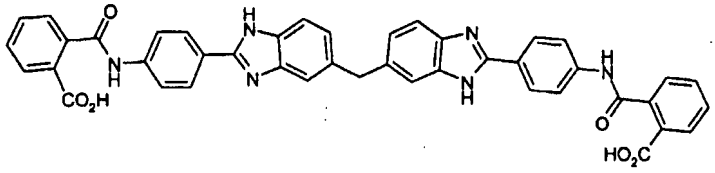

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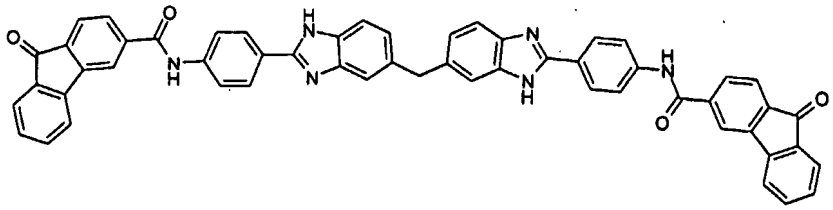

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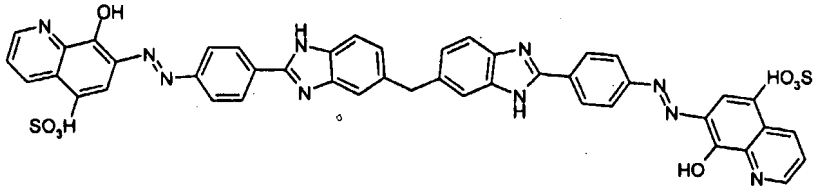

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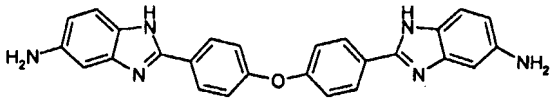

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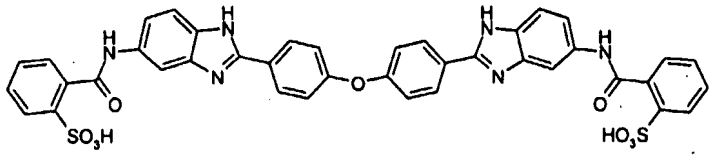

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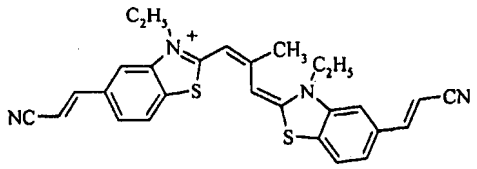

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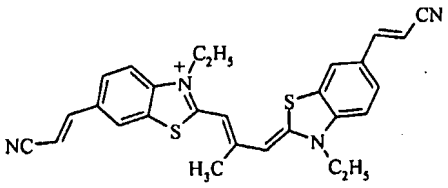

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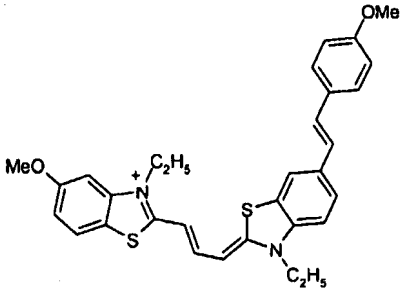

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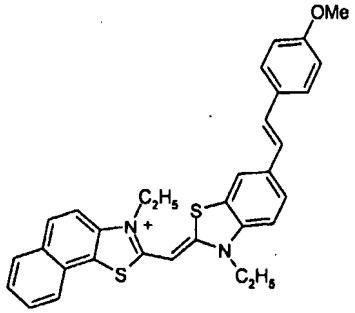

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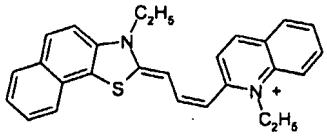

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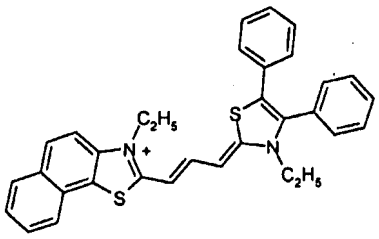

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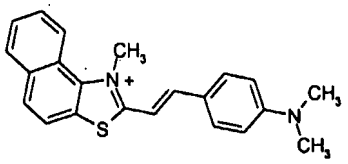

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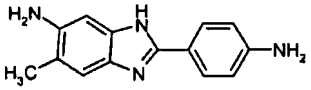

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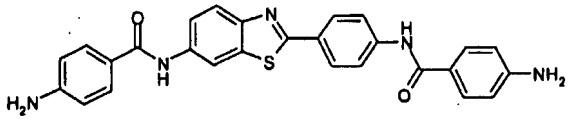

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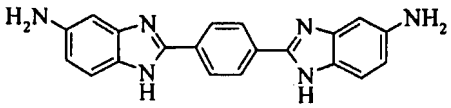
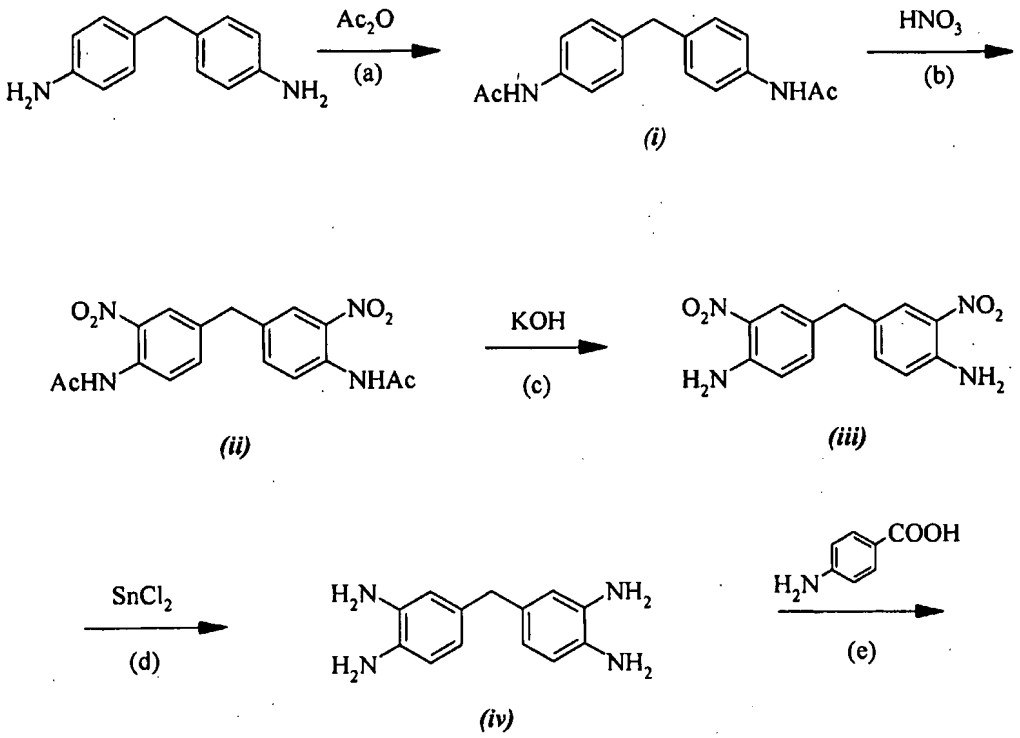
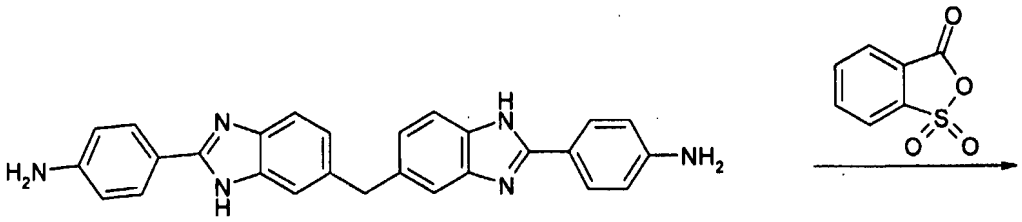


APPENDIX B - Schemes

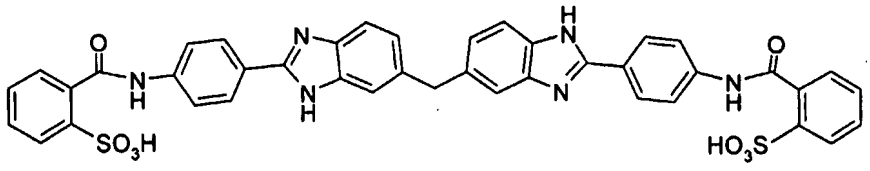


Compound 1

Scheme 1

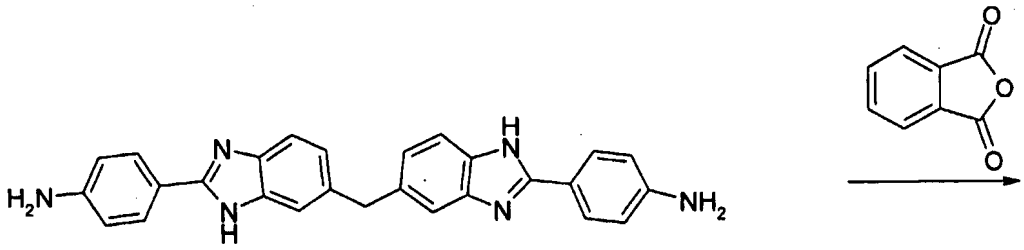


Compound 1

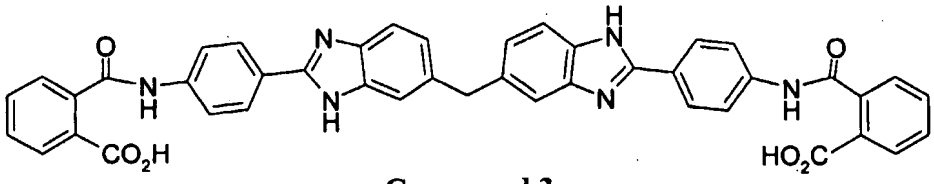


Compound 2

Scheme 2

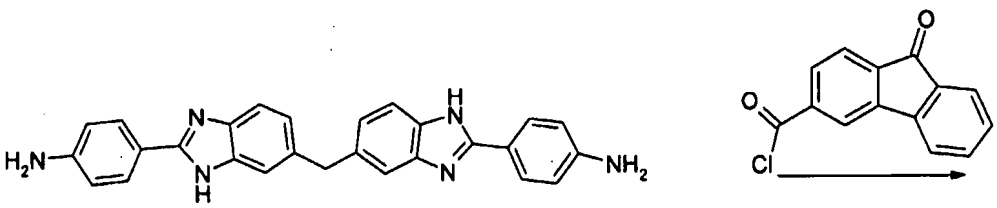


Compound 1

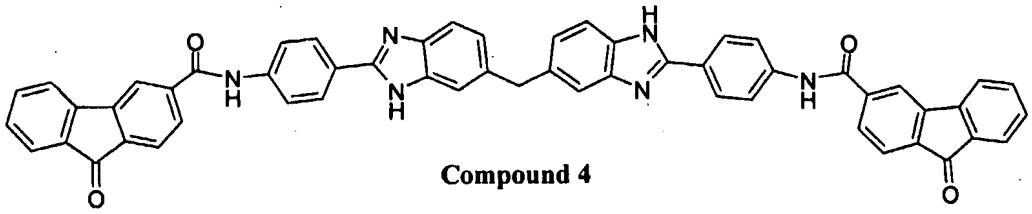


Compound 3

Scheme 3

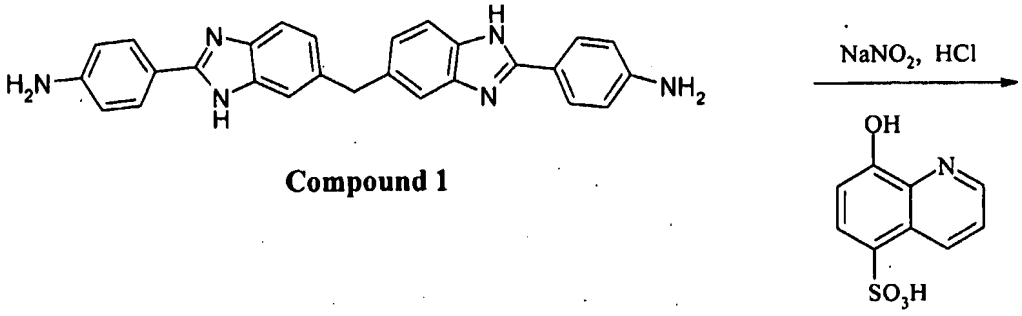


Compound 1

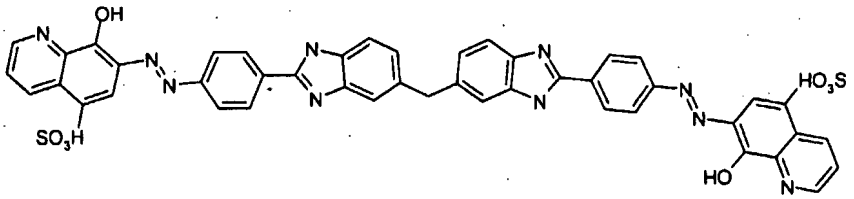


Compound 4

Scheme 4

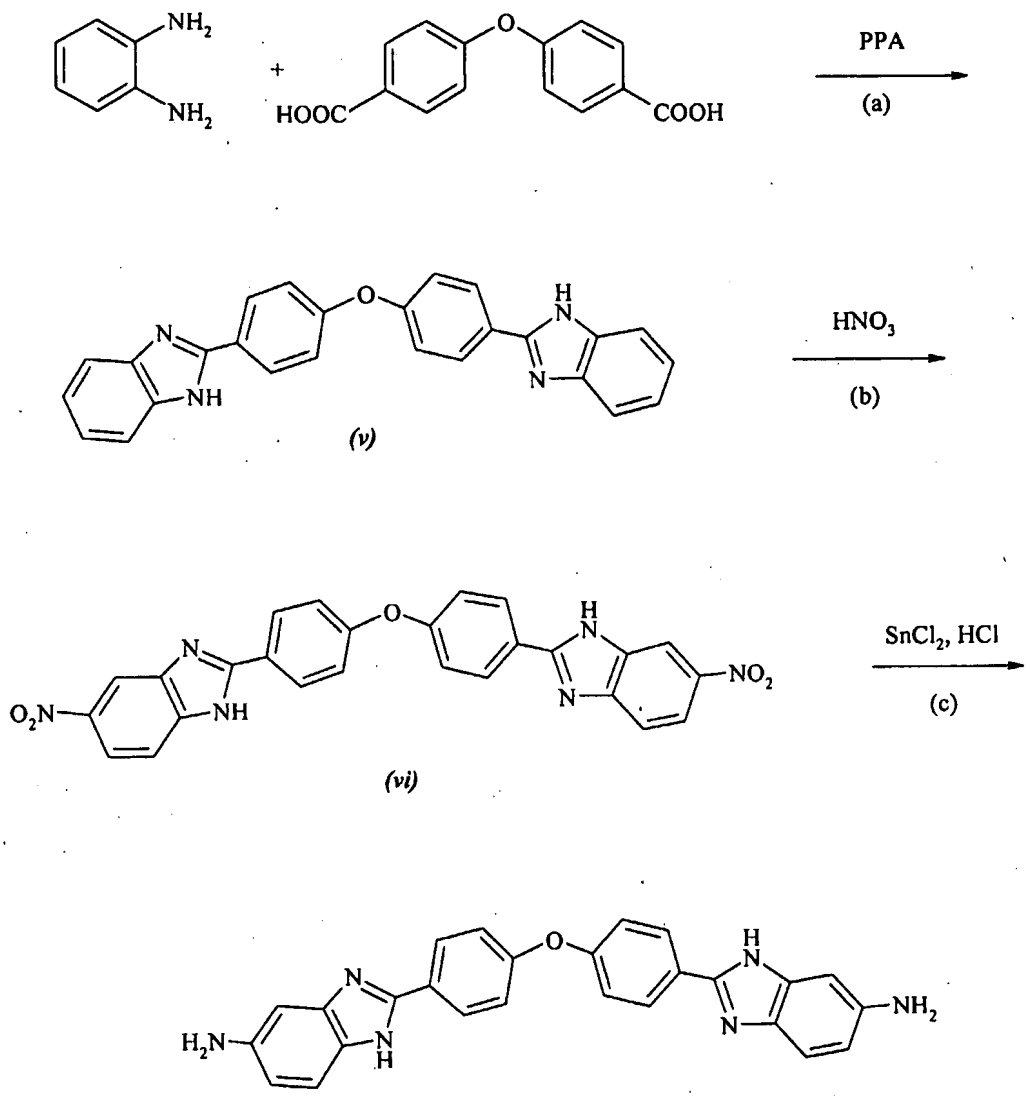


Compound 1



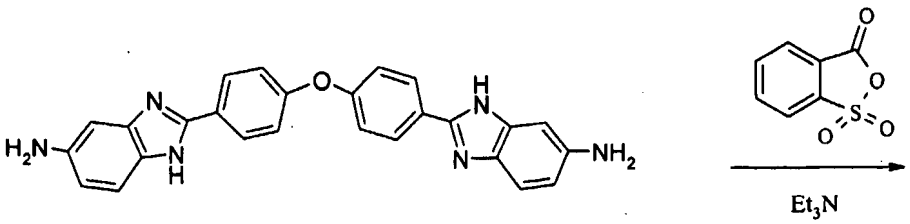
Compound 5

Scheme 5

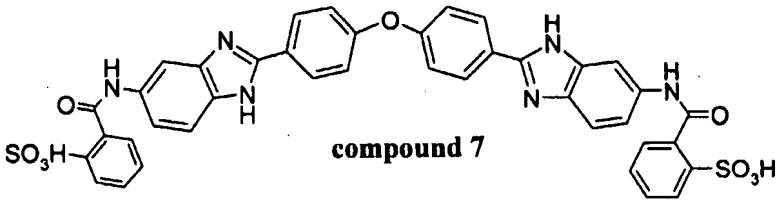


Compound 6

Scheme 6

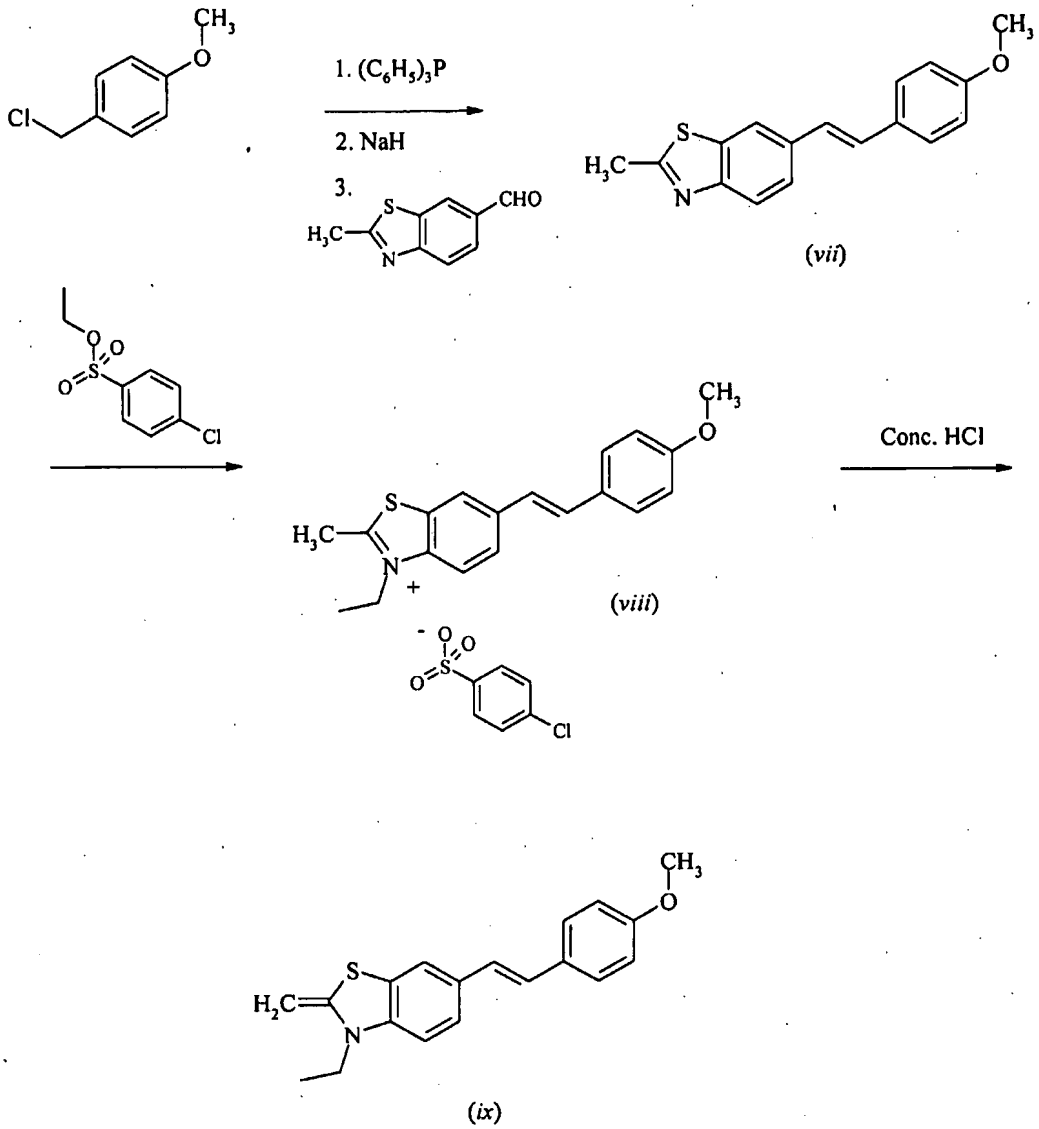


compound 6

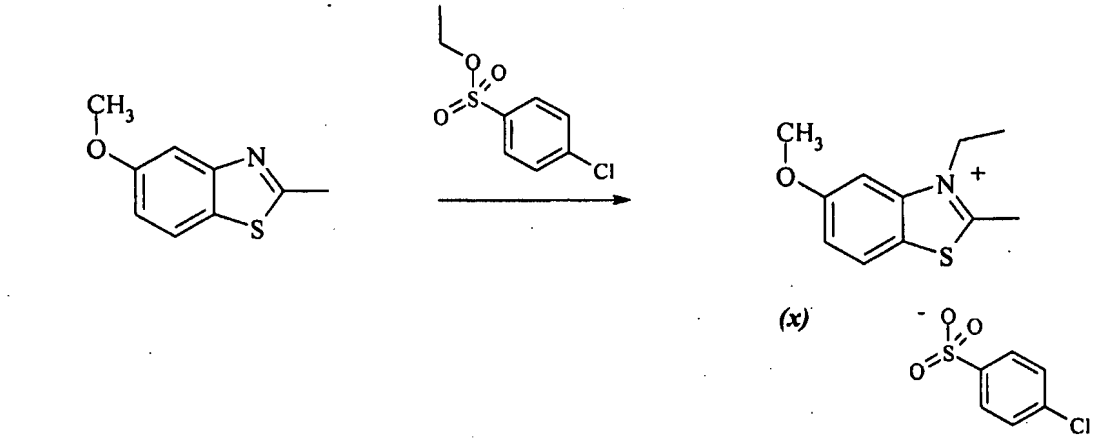


compound 7

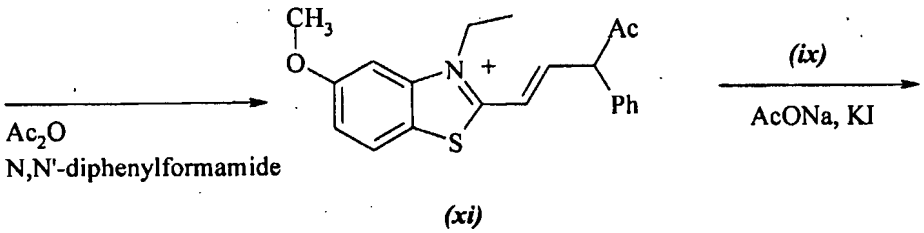
Scheme 7



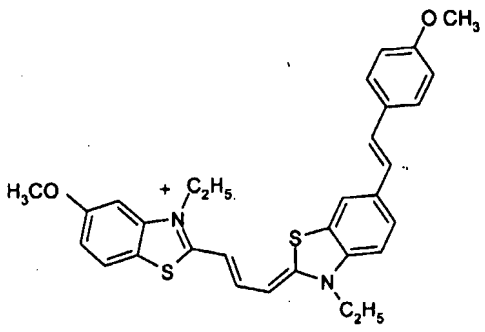
Scheme 8



(x)

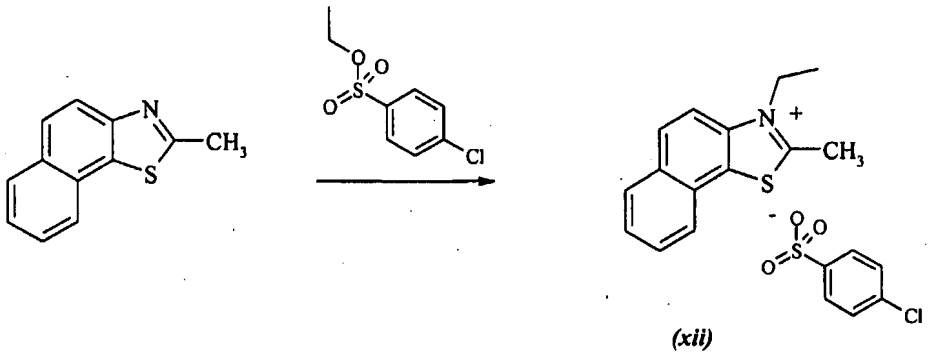


(xi)

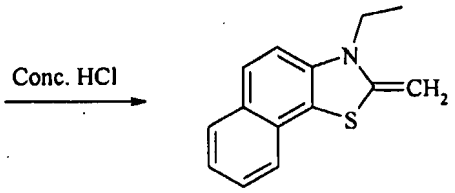


Compound 10

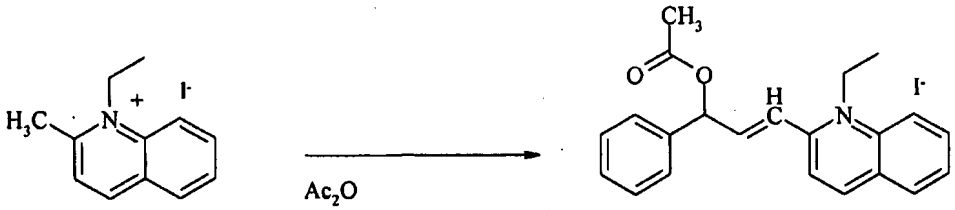
Scheme 9



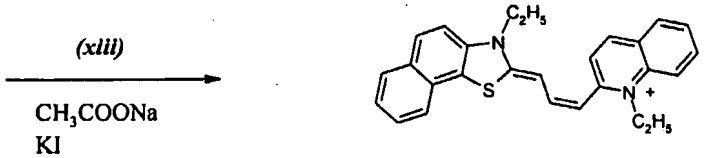
(xii)



(xiii)

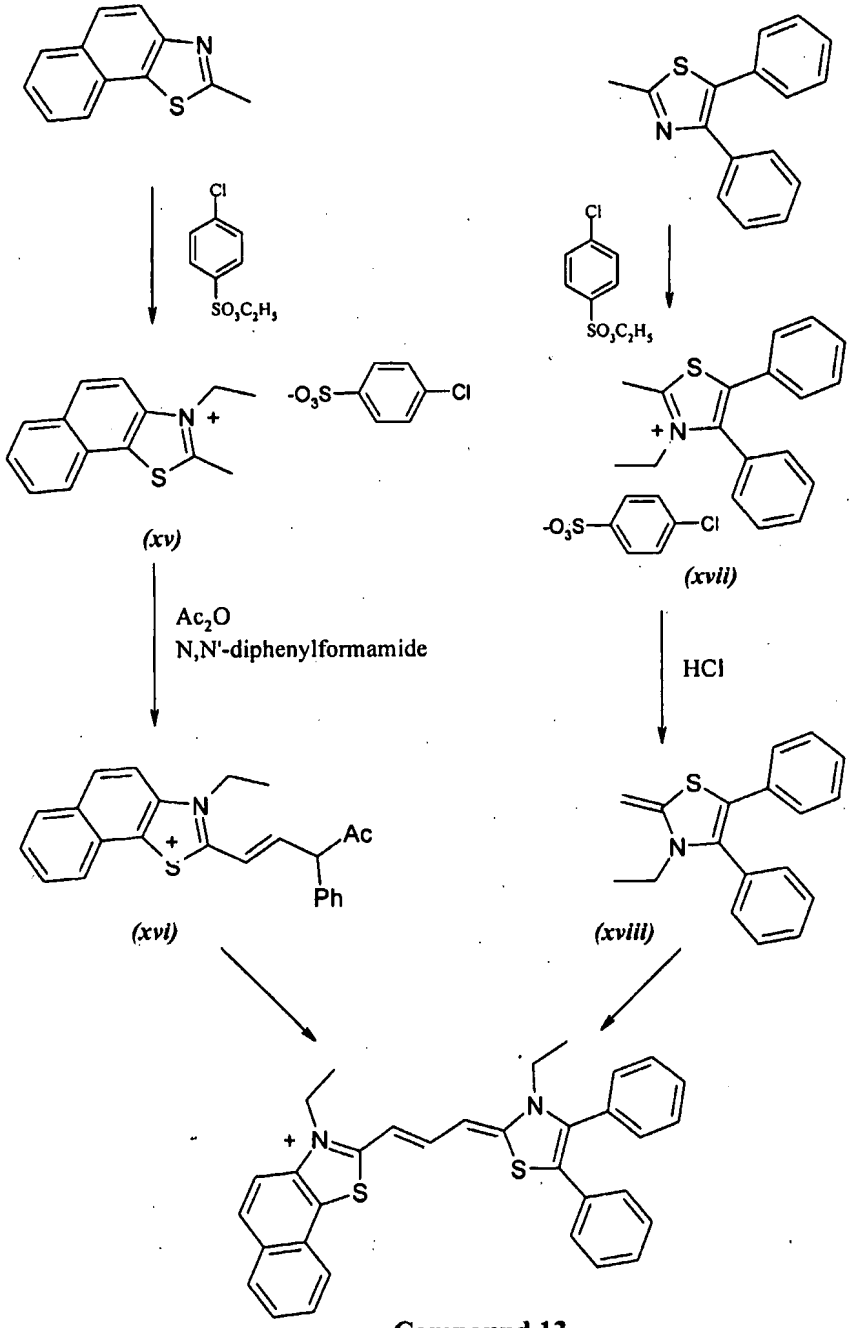


(xiv)



Compound 12

Scheme 10

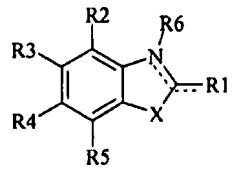


Compound 13

Scheme 11

CLAIMS:

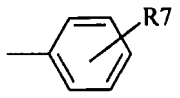
1. A pharmaceutical composition for treatment of diseases and disorders caused by or associated with heparanase catalytic activity, said composition comprising a pharmaceutically acceptable carrier and at least one heparanase inhibitor which is a benz-1,3-azole compound of the general Formula I:



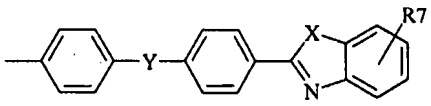
(I)

wherein

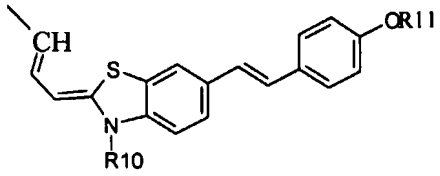
R1 is a radical selected from radicals (a)-(i):



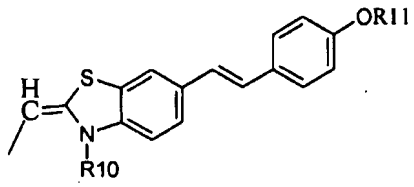
(a)



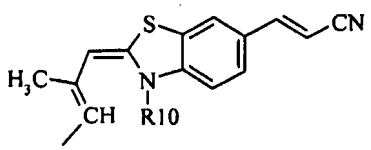
(b)

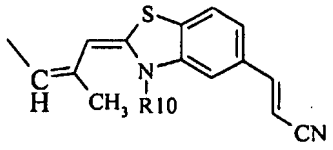


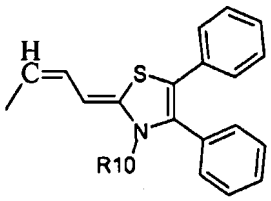
(c)

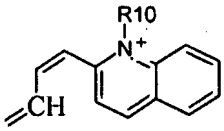


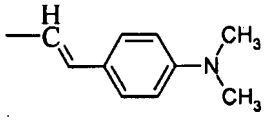
(d)


(e)


(f)


(g)


(h)


(i)

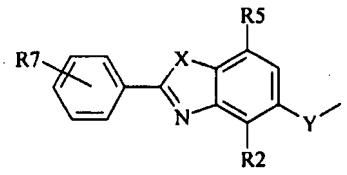
and wherein

R2 and R5 each independently represents hydrogen; halogen; -SO_3H; C1-C6 alkoxy optionally substituted by halogen or -SO_3H; C2-C6 alkenyl; C2-C7 alkanoyl; C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; C1-C6 alkylthio; or C6-C14 aryl;

R3 and R4 each independently represents hydrogen, methyl, ethyl, methoxy, ethoxy, nitro, -CH=CH-CN, or -NR8R9;

or R2 and R3 are both H and R4 and R5 together with the carbon atoms to which they are attached form a condensed benzene ring; or R4 and R5 are both H and R2 and R3 together with the carbon atoms to which they are attached form a condensed benzene ring;

or R3 is H and R4 is a radical of the formula (j):



(j)

and wherein in all formulas above:

X is NH, O or S;

Y is a direct bond, $-CH_2-$, -O-, -CO-, -SO-, $-SO_2-$ or -NR' where R' is C1-C6 alkyl optionally substituted with halogen, preferably fluoro; C2-C6 alkenyl or C6-C14 aryl;

R6 is absent or is C1-C6 alkyl or C2-C6 alkenyl, wherein said C1-C6 alkyl may optionally be substituted at the terminal carbon atom by –NR8R9 or -COOR, where R is H, C1-C6 alkyl, C2-C6 alkenyl or C6-C14 aryl;

R7 is hydrogen or at least one group selected from (i) halogen; (ii) nitro; (iii) -NR8R9; (iv) $-SO_3H$; (v) -OR12; (vi) -SR12; (vii) C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; (viii) C2-C6 alkenyl; (ix) C2-C7 alkanoyl; (x) C6-C14 aryl; (xi) –N=N-R" where R" is heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S and being optionally substituted by at least one radical selected from -OH, -COOH or $-SO_3H$; (xii) benzimidazol-2-yl; (xiii) benzthiazol-2-yl; or (xiv) benzoxazol-2-yl, said radicals (xii), (xiii) and (xiv) being optionally substituted by at least one radical selected from halogen, -NR8R9, $-SO_3H$, C1-C6 alkyl, C2-C6 alkenyl, C2-C7 alkanoyl, or C1-C6 alkoxy;

R8 and R9 each independently represents hydrogen or C1-C6 alkyl, or R8 is H and R9 is C2-C7 alkanoyl or C7-C15 aroyl optionally substituted by oxo, $-SO_3H$, -COOH, and/or $-NH_2$; or the radicals R8 and R9, together with the N atom to which they are attached, form a saturated 5-7 membered heterocyclic ring optionally containing at least one further heteroatom selected from O, S and/or N, said further N atom being optionally substituted by C1-C6 alkyl;

R10 is hydrogen; C1-C6 alkyl optionally substituted at the terminal carbon atom by -COOR wherein R is H, C1-C6 alkyl, C2-C6 alkenyl or aryl; or C2-C6 alkenyl;

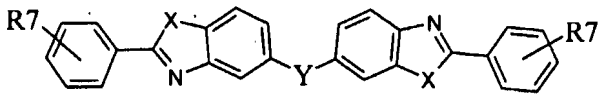
R11 is C1-C6 alkyl optionally substituted by fluoro; C1-C6 alkoxy; C1-C6 alkylthio; or -COOR wherein R is H, C1-C6 alkyl, C2-C6 alkenyl, or aryl;

R12 is C1-C6 alkyl or C2-C6 alkenyl;

and wherein the dotted lines indicate either a double bond stretching from the carbon atom at the 2 position of the benz-1,3-azole ring to the N atom at the ring in which case said N atom is positively charged when R6 is present, or the dotted line represents a double bond stretching from the carbon atom at the 2 position of the benz-1,3-azole ring to the first carbon atom of R1; and

pharmaceutically acceptable salts thereof.

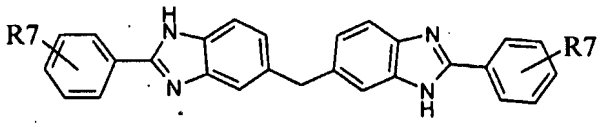
2. A pharmaceutical composition according to Claim 1 comprising a compound of the Formula Ia:



(Ia)

wherein X, Y and R7 are as defined in Claim 1.

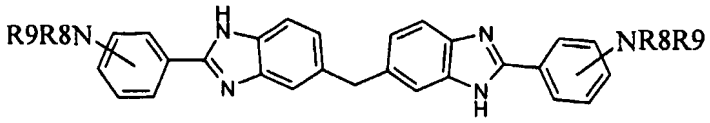
3. A pharmaceutical composition according to Claim 2 comprising a compound of the Formula Ib:



(Ib)

wherein R7 is as defined in Claim 1.

4. A pharmaceutical composition according to Claim 2 comprising a compound of the Formula Ic:

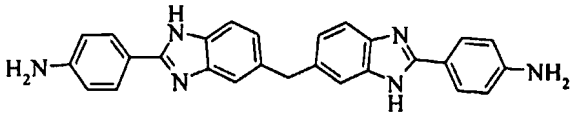


(Ic)

wherein R8 and R9 are as defined in Claim 1 and the phenyl radicals may be further substituted by (i) halogen; (ii) nitro; (iii) -NR8R9; (iv) -SO_3H; (v) -OR12; (vi) -SR12; (vii) C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; (viii) C2-C6 alkenyl; (ix) C2-C7 alkanoyl; (x) C6-C14 aryl; (xi) –N=N-R" where R" is heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S and being optionally substituted by at least one radical selected from -OH, -COOH or -SO_3H;

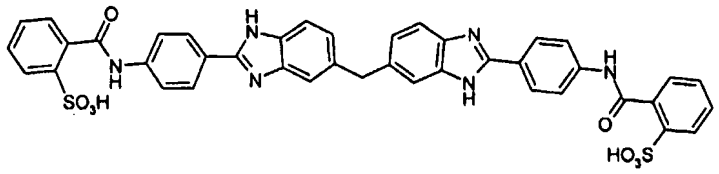
and R12 is C1-C6 alkyl or C2-C6 alkenyl.

5. A pharmaceutical composition according to Claim 4 comprising the compound herein designated **Compound 1** of the formula:

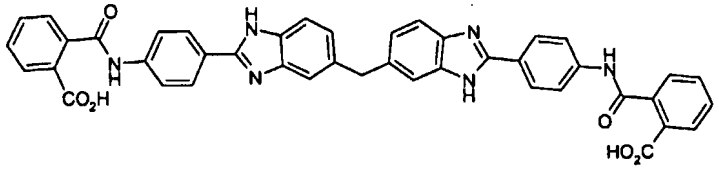


6. A pharmaceutical composition according to Claim 4 comprising a compound of the Formula Ic wherein R8 is H and R9 is benzoyl substituted at the ortho-position by -SO_3H or -COOH, or R9 is a 9-oxo-fluoren-3-oyl radical.

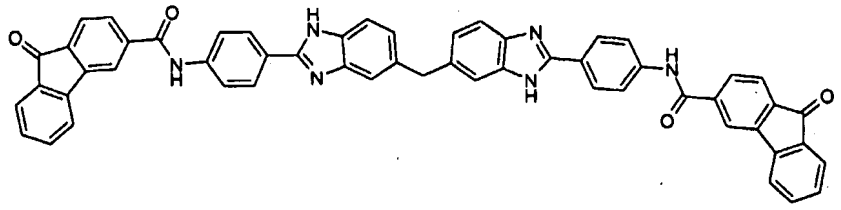
7. A pharmaceutical composition according to Claim 6 comprising the compound herein designated **Compound 2** of the formula:



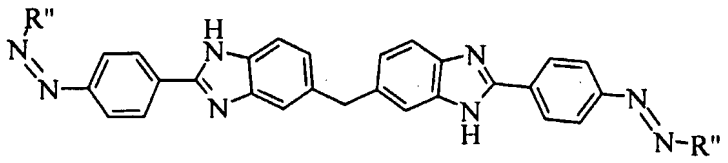
8. A pharmaceutical composition according to Claim 6 comprising the compound herein designated **Compound 3** of the formula:



9. A pharmaceutical composition according to Claim 6 comprising the compound herein designated **Compound 4** of the formula:



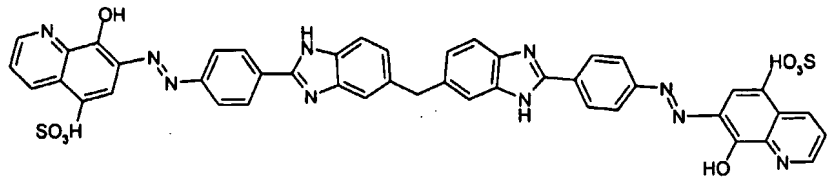
10. A pharmaceutical composition according to Claim 3 comprising a compound of the Formula Id:



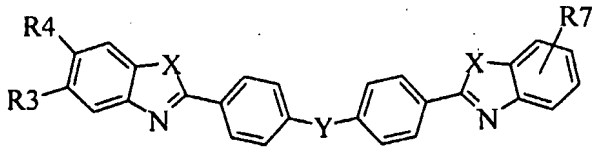
(Id)

wherein R" is a heteroaryl derived from a mono- or poly-cyclic heteroatomatic ring containing one to three heteroatoms selected from N, O and/or S and being optionally substituted by -OH, -COOH and/or -SO_3H.

11. A pharmaceutical composition according to Claim 10 comprising the compound herein designated **Compound 5** of the formula:



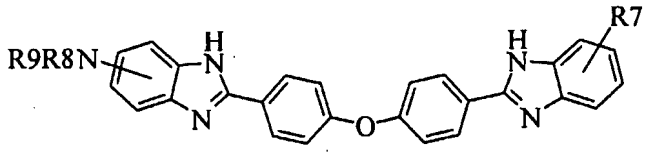
12. A pharmaceutical composition according to Claim 1 comprising a compound of the Formula Ie:



(Ie)

wherein R3 is H and R4 is –NR8R9 or R4 is H and R3 is –NR8R9, and X, Y and R7 are as defined in Claim 1.

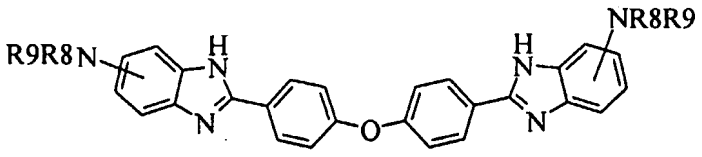
13. A pharmaceutical composition according to Claim 12 comprising a compound of the Formula If:



(If)

wherein R7, R8 and R9 are as defined in Claim 1.

14. A pharmaceutical composition according to Claim 12 comprising a compound of the Formula Ig:

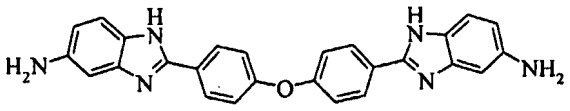


(Ig)

wherein R8 and R9 are as defined in Claim 1 and the phenyl radicals may be further substituted (i) halogen; (ii) nitro; (iii) -NR8R9; (iv) -SO_3H; (v) -OR12; (vi) -SR12; (vii) C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; (viii) C2-C6 alkenyl; (ix) C2-C7 alkanoyl; or (x) C6-C14 aryl;

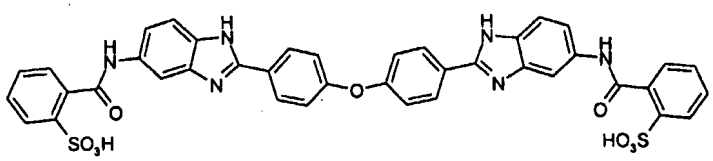
and R12 is C1-C6 alkyl or C2-C6 alkenyl.

15. A pharmaceutical composition according to Claim 14 comprising the compound herein designated **Compound 6** of the formula:

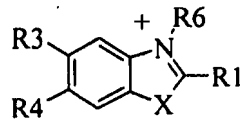


16. A pharmaceutical composition according to Claim 14 comprising a compound of the Formula Ig wherein R8 is H and R9 is benzoyl substituted at the ortho-position by -SO_3H.

17. A pharmaceutical composition according to Claim 16 comprising the compound herein designated **Compound 7** of the formula:



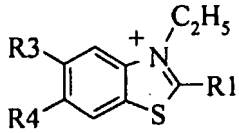
18. A pharmaceutical composition according to Claim 1 comprising a compound of the Formula Ih:



(Ih)

wherein X, R1, R3, and R4 are as defined in Claim 1 and R6 is C1-C6 alkyl.

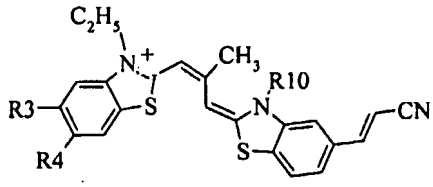
19. A pharmaceutical composition according to Claim 18 comprising a compound of the Formula Ii:



(Ii)

wherein R1, R3 and R4 are as defined in Claim 1.

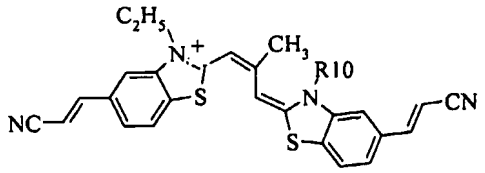
20. A pharmaceutical composition according to Claim 19 comprising a compound of the Formula Ij:



(Ij)

wherein R3, R4 and R10 are as defined in Claim 1.

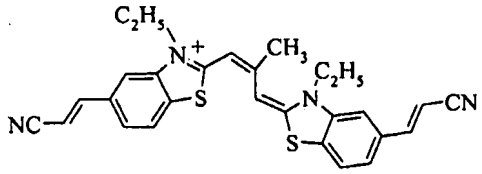
21. A pharmaceutical composition according to Claim 20 comprising a compound of the Formula Ik:



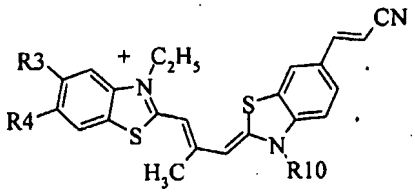
(Ik)

wherein R10 is as defined in Claim 1.

22. A pharmaceutical composition according to Claim 21 comprising the compound herein designated **Compound 8** of the formula:



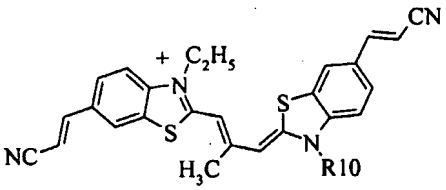
23. A pharmaceutical composition according to Claim 19 comprising a compound of the Formula Il:



(Il)

wherein R3, R4 and R10 are as defined in Claim 1.

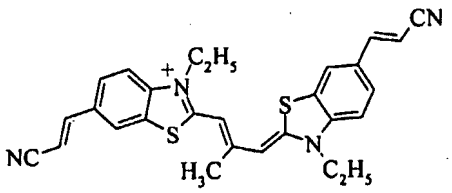
24. A pharmaceutical composition according to Claim 23 comprising a compound of the Formula Im:



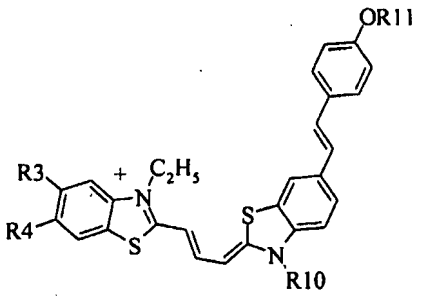
(Im)

wherein R10 is as defined in Claim 1.

25. A pharmaceutical composition according to Claim 24 comprising the compound herein designated **Compound 9** of the formula:



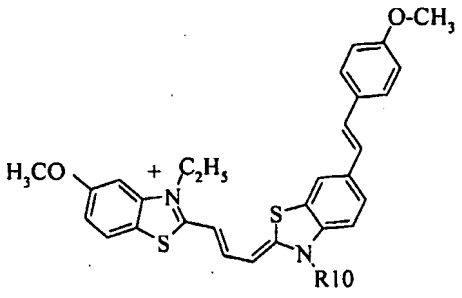
26. A pharmaceutical composition according to Claim 19 comprising a compound of the Formula In:



(In)

wherein R3, R4, R10 and R11 are as defined in Claim 1.

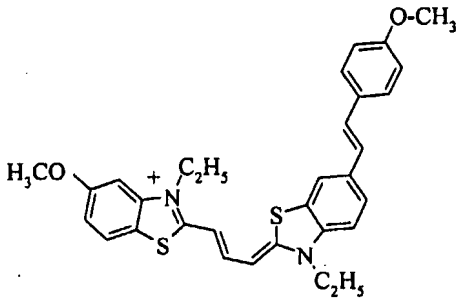
27. A pharmaceutical composition according to Claim 26 comprising a compound of the Formula Io:



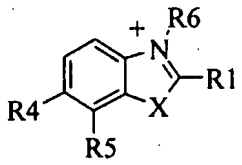
(Io)

wherein R10 is as defined in Claim 1.

28. A pharmaceutical composition according to Claim 27 comprising the compound herein designated **Compound 10** of the formula:



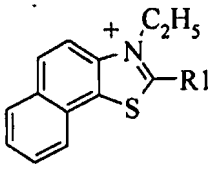
29. A pharmaceutical composition according to Claim 1 comprising a compound of the Formula Ip:



(Ip)

wherein X, R1, R4, R5 and R6 are as defined in Claim 1.

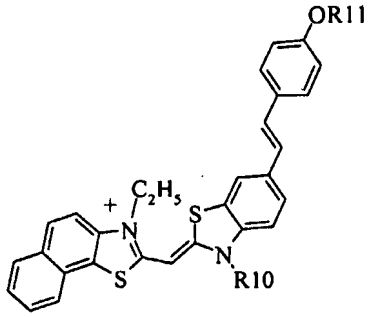
30. A pharmaceutical composition according to Claim 29 comprising a compound of the Formula Iq:



(Iq)

wherein R1 is as defined in Claim 1.

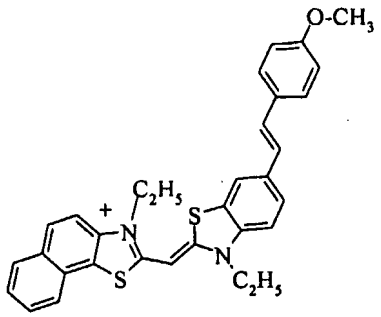
31. A pharmaceutical composition according to Claim 30 comprising a compound of the Formula Ir:



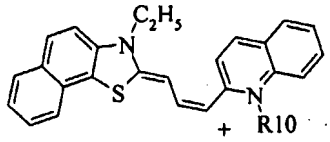
(Ir)

wherein R10 and R11 are as defined in Claim 1.

32. A pharmaceutical composition according to Claim 31 comprising the compound herein designated **Compound 11** of the formula:



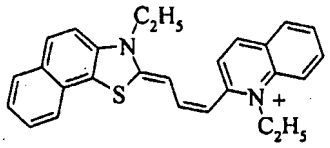
33. A pharmaceutical composition according to Claim 1 comprising a compound of the Formula Is:



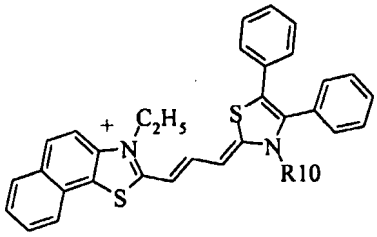
(Is)

wherein R10 is as defined in Claim 1.

34. A pharmaceutical composition according to Claim 33 comprising the compound herein designated **Compound 12** of the formula:



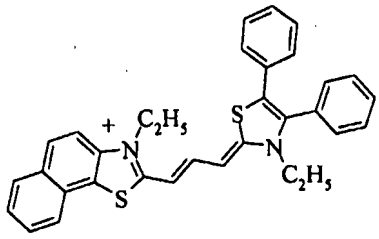
35. A pharmaceutical composition according to Claim 29 comprising a compound of the Formula It:



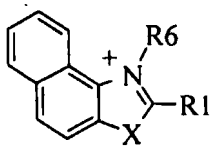
(It)

wherein R10 is as defined in Claim 1.

36. A pharmaceutical composition according to Claim 35 comprising the compound herein designated **Compound 13** of the formula:



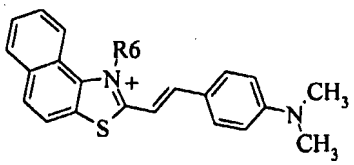
37. A pharmaceutical composition according to Claim 1 comprising a compound of the Formula Iu:



(Iu)

wherein X, R1 and R6 are as defined in Claim 1.

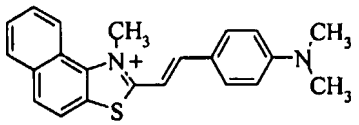
38. A pharmaceutical composition according to Claim 37 comprising a compound of the Formula Iv:



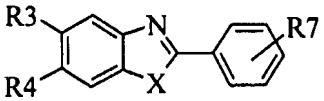
(Iv)

wherein R6 is C1-C6 alkyl.

39. A pharmaceutical composition according to Claim 38 comprising the compound herein designated **Compound 14** of the formula:



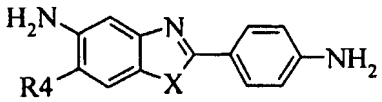
40. A pharmaceutical composition according to Claim 1 comprising a compound of the Formula Iw:



(Iw)

wherein R3 and R7 are -NR8R9, wherein R4, R8 and R9 are as defined in Claim 1.

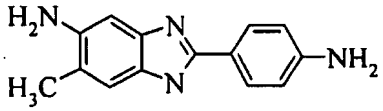
41. A pharmaceutical composition according to Claim 40 comprising a compound of the Formula Ix:



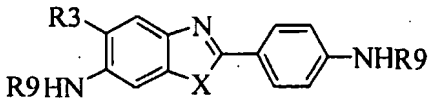
(Ix)

wherein X and R4 are as defined in Claim 1.

42. A pharmaceutical composition according to Claim 41 comprising the compound herein designated **Compound 15** of the formula:



43. A pharmaceutical composition according to Claim 41 comprising a compound of the Formula Iy:

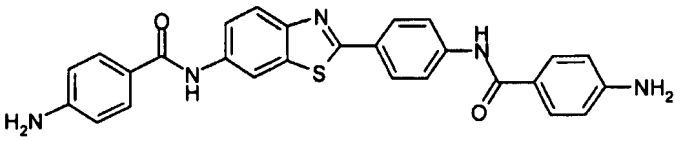


(Iy)

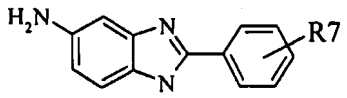
wherein X, R3 and R9 are as defined in Claim 1.

44. A pharmaceutical composition according to Claim 43 comprising a compound of the Formula Iy wherein X is S, and R9 is benzoyl substituted by $-NH_2$.

45. A pharmaceutical composition according to Claim 44 comprising the compound herein designated **Compound 16** of the formula:



46. A pharmaceutical composition according to Claim 40 comprising a compound of the Formula Iz:



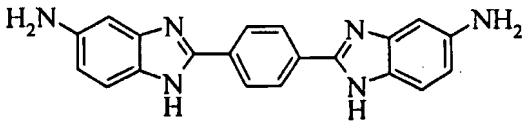
(Iz)

wherein R7 is as defined in Claim 1.

47. A pharmaceutical composition according to Claim 46 comprising a compound of the Formula Iz wherein R7 is selected from benzimidazol-2-yl, benzthiazol-2-yl, and benzoxazol-2-yl, said benzimidazol-2-yl, benzthiazol-2-yl, and benzoxazol-2-yl being optionally substituted by halogen, -NR8R9, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, C2-C7 alkanoyl, or C1-C6 alkoxy.

48. A pharmaceutical composition according to Claim 47 comprising a compound of the Formula Iz, wherein R7 is benzimidazolyl-2-yl, benthiazol-2-yl, or benzoxazol-2-yl substituted by -NH_2.

49. A pharmaceutical composition according to Claim 48 comprising the compound herein designated **Compound 17** of the formula:



50. A pharmaceutical composition according to any one of claims 1 to 49 for inhibition of angiogenesis.

51. A pharmaceutical composition according to any one of claims 1 to 49 for treatment or inhibition of a malignant cell proliferative disease or disorder.

52. The pharmaceutical composition according to claim 50 or 51 for the treatment or inhibition of non-solid cancers, e.g hematopoietic malignancies such as all types of leukemia, e.g. acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), myelodysplastic syndrome (MDS), mast cell leukemia, hairy cell leukemia, Hodgkin's disease, non-Hodgkin's lymphomas, Burkitt's lymphoma and multiple myeloma.

53. The pharmaceutical composition according to claim 50 or 51 for the treatment or inhibition of solid tumors such as tumors in lip and oral cavity, pharynx, larynx, paranasal sinuses, major salivary glands, thyroid gland, esophagus, stomach, small intestine, colon, colorectum, anal canal, liver, gallbladder, extrahepatic bile ducts, ampulla of vater, exocrine pancreas, lung, pleural mesothelioma, bone, soft tissue sarcoma, carcinoma and malignant melanoma of the skin, breast, vulva, vagina, cervix uteri, corpus uteri, ovary, fallopian tube, gestational trophoblastic tumors, penis, prostate, testis, kidney, renal pelvis, ureter, urinary bladder, urethra, carcinoma of the eyelid, carcinoma of the conjunctiva, malignant melanoma of the conjunctiva, malignant melanoma of the uvea, retinoblastoma, carcinoma of the lacrimal gland, sarcoma of the orbit, brain, spinal cord, vascular system, hemangiosarcoma and Kaposi's sarcoma.

54. The pharmaceutical composition according to claim 52 or 53 for treating or inhibiting tumor formation, primary tumors, tumor progression or tumor metastasis.

55. A pharmaceutical composition according to any one of claims 1 to 50 for treatment of ophthalmologic disorders such as diabetic retinopathy and macular degeneration, particularly age-related macular degeneration.

56. The pharmaceutical composition according to any one of claims 1 to 49 for inhibiting or treating cell proliferative diseases or disorders such as psoriasis, hypertrophic scars, acne and sclerosis/scleroderma.

57. The pharmaceutical composition according to any one of claims 1 to 49 for inhibiting or treatment of a disease or disorder selected from polyps, multiple exostosis, hereditary exostosis, retrolental fibroplasia, hemangioma, reperfusion of gastric ulcer and arteriovenous malformation.

58. The pharmaceutical composition according to any one of claims 1 to 49, for contraception or for inducing abortion at early stages of pregnancy.

59. The pharmaceutical composition according to any one of claims 1 to 49, for treatment of or amelioration of inflammatory symptoms in any disease, condition or disorder where immune and/or inflammation suppression is beneficial.

60. The pharmaceutical composition according to claim 59, for treatment of or amelioration of inflammatory symptoms in the joints, musculoskeletal and connective tissue disorders.

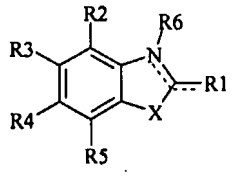
61. The pharmaceutical composition according to claim 59, for treatment of or amelioration of inflammatory symptoms associated with hypersensitivity, allergic reactions, asthma, atherosclerosis, otitis and other otorhinolaryngological diseases, dermatitis and other skin diseases, posterior and anterior uveitis, conjunctivitis, optic neuritis, scleritis and other immune and/or inflammatory ophthalmic diseases.

62. The pharmaceutical composition according to any one of claims 1 to 49, for treatment of or amelioration of an autoimmune disease.

63. The pharmaceutical composition according to claim 62, wherein said autoimmune disease is Eaton-Lambert syndrome, Goodpasture's syndrome, Grave's disease, Guillain-Barré sundrome, autoimmune hemolytic anemia (AIHA), hepatitis, insulin-dependent diabetes mellitus (IDDM), systemic lupus erythematosus (SLE), multiple sclerosis (MS), myasthenia gravis, plexus disorders e.g. acute brachial neuritis,, polyglandular deficiency syndrome, primary biliary cirrhosis, rheumatoid arthritis, scleroderma, thrombocytopenia,

thyroiditis e.g. Hashimoto's disease, Sjögren's syndrome, allergic purpura, psoriasis, mixed connective tissue disease, polymyositis, dermatomyositis, vasculitis, polyarteritis nodosa, polymyalgia rheumatica, Wegener's granulomatosis, Reiter's syndrome, Behçet's syndrome, ankylosing spondylitis, pemphigus, bullous pemphigoid, dermatitis herpetiformis, Crohn's disease and autism.

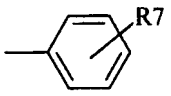
64. Use of a benz-1,3-azole compound of the general Formula I:



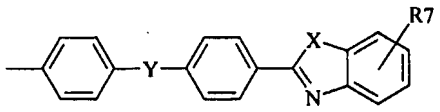
(I)

wherein

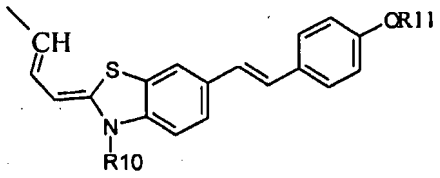
R1 is a radical selected from radicals (a)-(i):



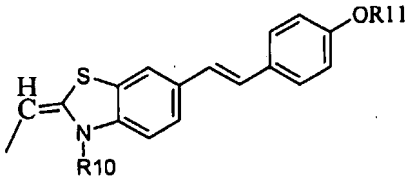
(a)



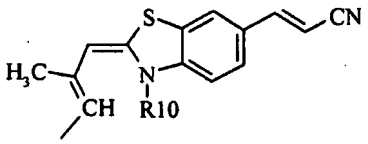
(b)



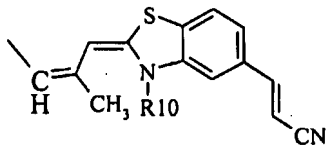
(c)



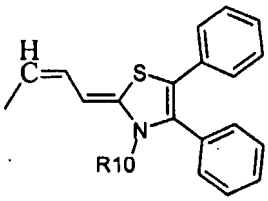
(d)



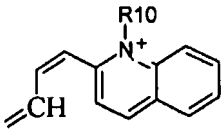
(e)



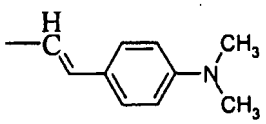
(f)



(g)



(h)



(i)

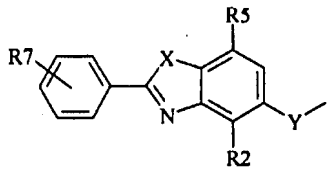
and wherein

R2 and R5 each independently represents hydrogen; halogen; $-SO_3H$; C1-C6 alkoxy optionally substituted by halogen or $-SO_3H$; C2-C6 alkenyl; C2-C7 alkanoyl; C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; C1-C6 alkylthio; or C6-C14 aryl;

R3 and R4 each independently represents hydrogen, methyl, ethyl, methoxy, ethoxy, nitro, -CH=CH-CN, or -NR8R9;

or R2 and R3 are both H and R4 and R5 together with the carbon atoms to which they are attached form a condensed benzene ring; or R4 and R5 are both H and R2 and R3 together with the carbon atoms to which they are attached form a condensed benzene ring;

or R3 is H and R4 is a radical of the formula (j):



(j)

and wherein in all formulas above:

X is NH, O or S;

Y is a direct bond, $-CH_2-$, -O-, -CO-, -SO-, $-SO_2-$ or -NR' where R' is C1-C6 alkyl optionally substituted with halogen, preferably fluoro; C2-C6 alkenyl or C6-C14 aryl;

R6 is absent or is C1-C6 alkyl or C2-C6 alkenyl, wherein said C1-C6 alkyl may optionally be substituted at the terminal carbon atom by –NR8R9 or -COOR, where R is H, C1-C6 alkyl, C2-C6 alkenyl or C6-C14 aryl;

R7 is hydrogen or at least one group selected from (i) halogen; (ii) nitro; (iii) -NR8R9; (iv) $-SO_3H$; (v) -OR12; (vi) -SR12; (vii) C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; (viii) C2-C6 alkenyl; (ix) C2-C7 alkanoyl; (x) C6-C14 aryl; (xi) –N=N-R" where R" is heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S and being optionally substituted by at least one radical selected from -OH, -COOH or $-SO_3H$; (xii) benzimidazol-2-yl; (xiii) benzthiazol-2-yl; or (xiv) benzoxazol-2-yl, said radicals (xii), (xiii) and (xiv) being optionally substituted by at least one radical selected from halogen, -NR8R9, $-SO_3H$, C1-C6 alkyl, C2-C6 alkenyl, C2-C7 alkanoyl, or C1-C6 alkoxy;

R8 and R9 each independently represents hydrogen or C1-C6 alkyl, or R8 is H and R9 is C2-C7 alkanoyl or C7-C15 aroyl optionally substituted by oxo, $-SO_3H$, -COOH, and/or $-NH_2$; or the radicals R8 and R9, together with the N atom to which they are attached, form a saturated 5-7 membered heterocyclic ring optionally containing at least one further

heteroatom selected from O, S and/or N, said further N atom being optionally substituted by C1-C6 alkyl;

R10 is hydrogen; C1-C6 alkyl optionally substituted at the terminal carbon atom by -COOR wherein R is H, C1-C6 alkyl, C2-C6 alkenyl or aryl; or C2-C6 alkenyl;

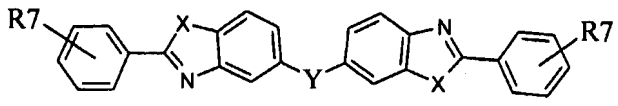
R11 is C1-C6 alkyl optionally substituted by fluoro; C1-C6 alkoxy; C1-C6 alkylthio; or -COOR wherein R is H, C1-C6 alkyl, C2-C6 alkenyl, or aryl;

R12 is C1-C6 alkyl or C2-C6 alkenyl;

and wherein the dotted lines indicate either a double bond stretching from the carbon atom at the 2 position of the benz-1,3-azole ring to the N atom at the ring in which case said N atom is positively charged when R6 is present, or the dotted line represents a double bond stretching from the carbon atom at the 2 position of the benz-1,3-azole ring to the first carbon atom of R1;

or of a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition which inhibits heparanase activity and is useful in the treatment of a disease or disorder caused by or associated with heparanase catalytic activity.

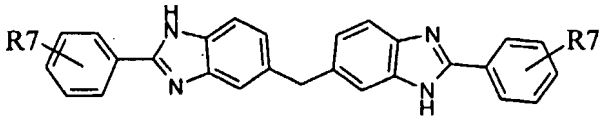
65. Use according to Claim 64 of a compound of the Formula Ia:



(Ia)

wherein X, Y and R7 are as defined in Claim 64.

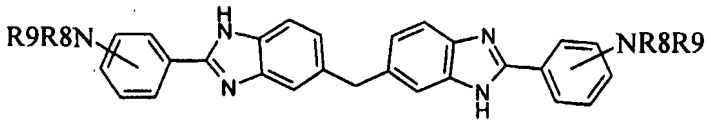
66. Use according to Claim 65 of a compound of the Formula Ib:



(Ib)

wherein R7 is as defined in Claim 64.

67. Use according to Claim 65 of a compound of the Formula Ic:

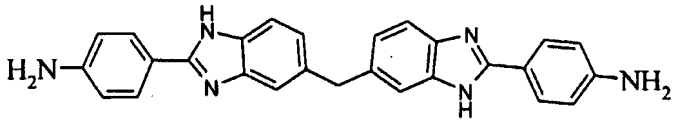


(Ic)

wherein R8 and R9 are as defined in Claim 64 and the phenyl radicals may be further substituted by (i) halogen; (ii) nitro; (iii) -NR8R9; (iv) -SO_3H; (v) -OR12; (vi) -SR12; (vii) C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; (viii) C2-C6 alkenyl; (ix) C2-C7 alkanoyl; (x) C6-C14 aryl; (xi) –N=N-R" where R" is heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S and being optionally substituted by at least one radical selected from -OH, -COOH or -SO_3H;

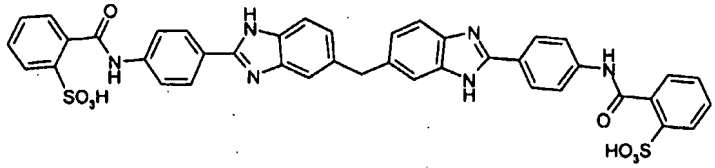
and R12 is C1-C6 alkyl or C2-C6 alkenyl.

68. Use according to Claim 67 of the compound herein designated **Compound 1** of the formula:

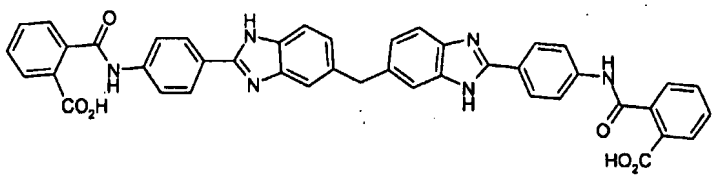


69. Use according to Claim 67 of a compound of the Formula Ic wherein R8 is H and R9 is benzoyl substituted at the ortho-position by -SO_3H or -COOH, or R9 is a 9-oxo-fluoren-3-oyl radical.

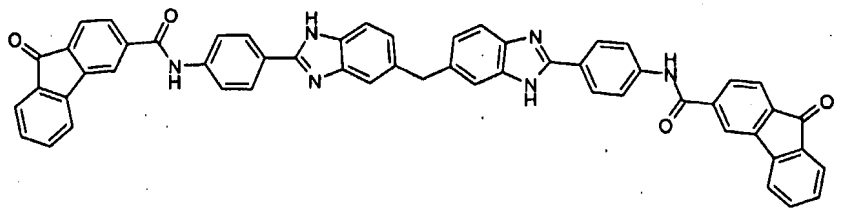
70. Use according to Claim 69 of the compound herein designated **Compound 2** of the formula:



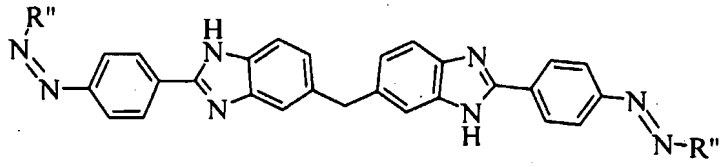
71. Use according to Claim 69 of the compound herein designated **Compound 3** of the formula:



72. Use according to Claim 69 of the compound herein designated **Compound 4** of the formula:



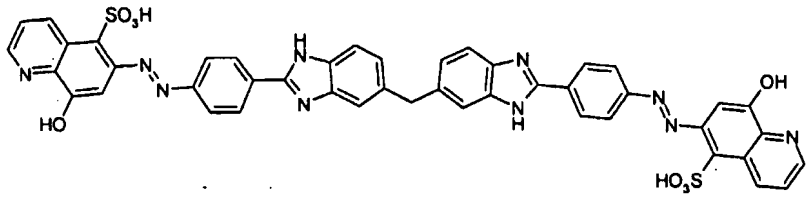
73. Use according to Claim 66 of a compound of the Formula Id:



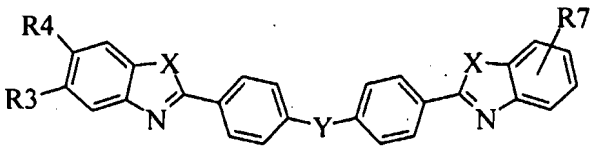
(Id)

wherein R" is a heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S and being optionally substituted by -OH, -COOH and/or $-SO_3H$.

74. Use according to Claim 73 of the compound herein designated **Compound 5** of the formula:



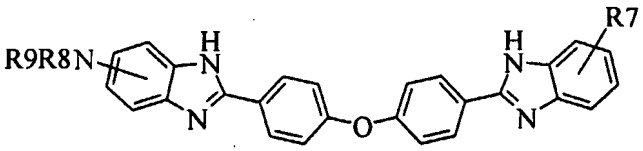
75. Use according to Claim 64 of a compound of the Formula Ie:



(Ie)

wherein X, Y and R7 are as defined in Claim 64.

76. A pharmaceutical composition according to Claim 75 of a compound of the Formula

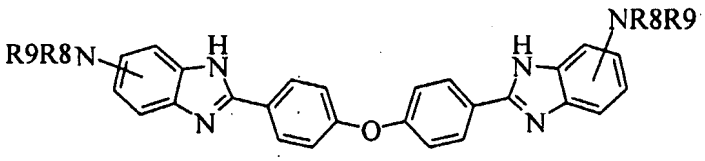


(If)

If:

wherein R7 is as defined in Claim 64.

77. Use according to Claim 75 of a compound of the Formula Ig:



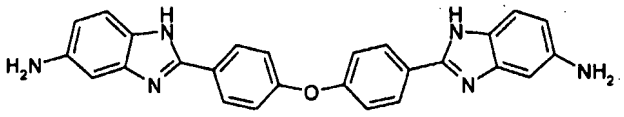
(Ig)

wherein R8 and R9 are as defined in Claim 1 and the phenyl radicals may be further substituted by (i) halogen; (ii) nitro; (iii) -NR8R9; (iv) -SO_3H; (v) -OR12; (vi) -SR12; (vii)

C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; (viii) C2-C6 alkenyl; (ix) C2-C7 alkanoyl; or (x) C6-C14 aryl;

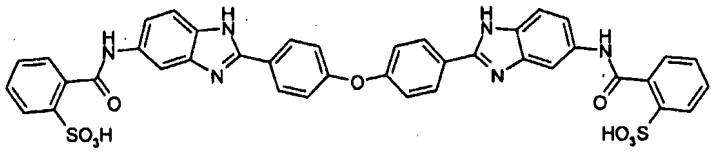
and R12 is C1-C6 alkyl or C2-C6 alkenyl.

78. Use according to Claim 77 of the compound herein designated **Compound 6** of the formula:

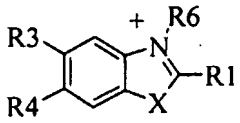


79. Use according to Claim 77 of a compound of the Formula Ig wherein R8 is H and R9 is benzoyl substituted at the ortho-position by $-SO_3H$.

80. Use according to Claim 79 of the compound herein designated Compound 7 of the formula:



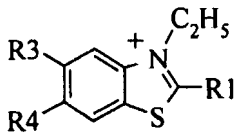
81. Use according to Claim 64 of a compound of the Formula Ih:



(Ih)

wherein X, R1, R3, and R4 are as defined in Claim 64 and R6 is C1-C6 alkyl.

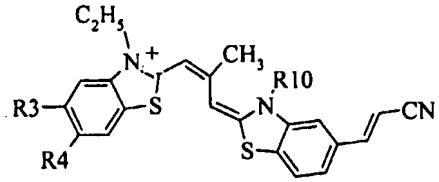
82. Use according to Claim 81 of a compound of the Formula Ii:



(Ii)

wherein R1, R3 and R4 are as defined in Claim 64.

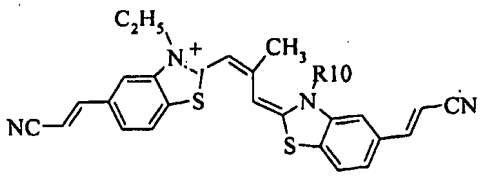
83. Use according to Claim 82 of a compound of the Formula Ij:



(Ij)

wherein R3, R4 and R10 are as defined in Claim 64.

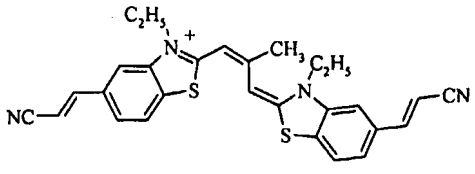
84. Use according to Claim 83 of a compound of the Formula Ik:



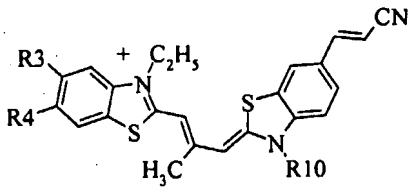
(Ik)

wherein R10 is as defined in Claim 64.

85. Use according to Claim 84 of the compound herein designated **Compound 8** of the formula:



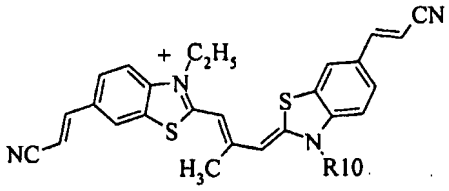
86. Use according to Claim 82 of a compound of the Formula II:



(II)

wherein R3, R4 and R10 are as defined in Claim 64.

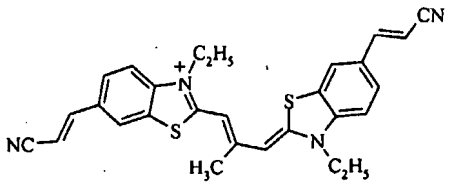
87. Use according to Claim 86 of a compound of the Formula Im:



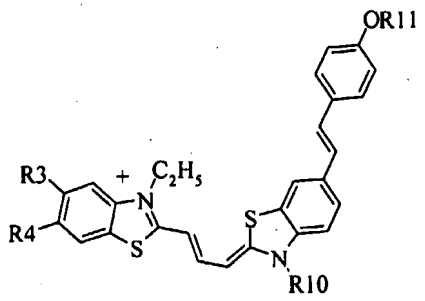
(Im)

wherein R10 is as defined in Claim 64.

88. Use according to Claim 87 of the compound herein designated **Compound 9** of the formula:



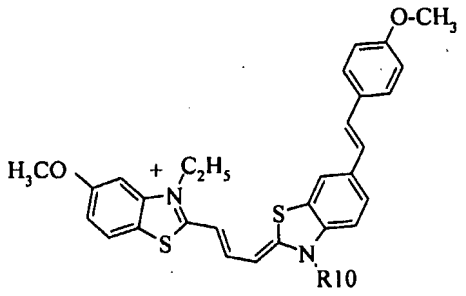
89. Use according to Claim 82 of a compound of the Formula In:



(In)

wherein R3, R4, R10 and R11 are as defined in Claim 64.

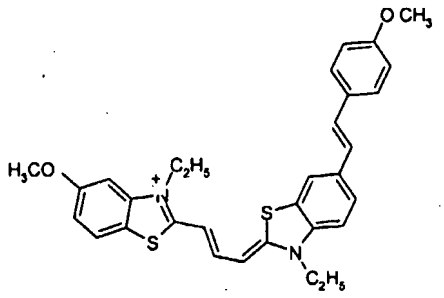
90. Use according to Claim 89 of a compound of the Formula Io:



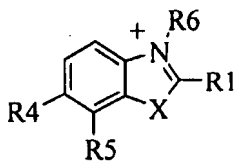
(Io)

wherein R10 is as defined in Claim 64.

91. Use according to Claim 90 of the compound herein designated **Compound 10** of the formula:



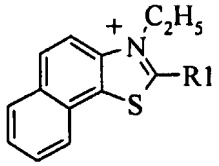
92. Use according to Claim 64 of a compound of the Formula Ip:



(Ip)

wherein X, R1, R4, R5 and R6 are as defined in Claim 64.

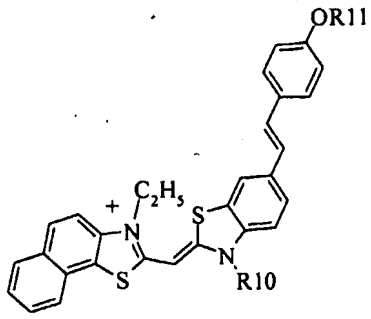
93. Use according to Claim 92 of a compound of the Formula Iq:



(Iq)

wherein R1 is as defined in Claim 64.

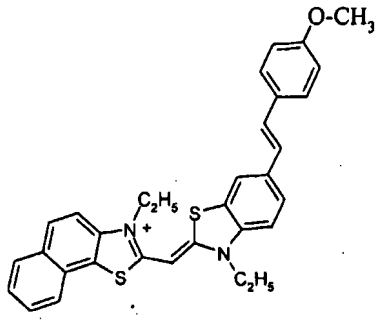
94. Use according to Claim 93 of a compound of the Formula Ir:



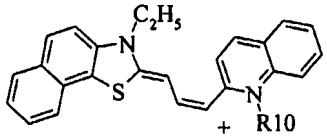
(Ir)

wherein R10 and R11 are as defined in Claim 64.

95. Use according to Claim 94 of the compound herein designated **Compound 11** of the formula:



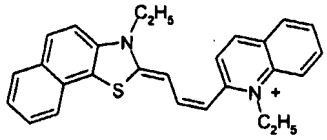
96. Use according to Claim 64 comprising a compound of the Formula Is:



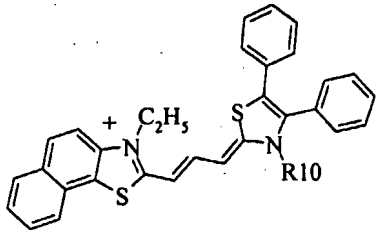
(Is)

wherein R10 is as defined in Claim 64.

97. Use according to Claim 96 of the compound herein designated **Compound 12** of the formula:



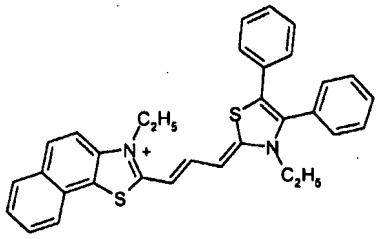
98. Use according to Claim 92 of a compound of the Formula It:



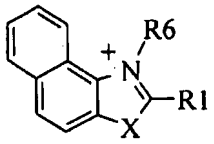
(It)

wherein R10 is as defined in Claim 64.

99. Use according to Claim 98 of the compound herein designated **Compound 13** of the formula:



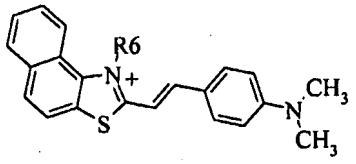
100. Use according to Claim 64 of a compound of the Formula Iu:



(Iu)

wherein X, R1 and R6 are as defined in Claim 64.

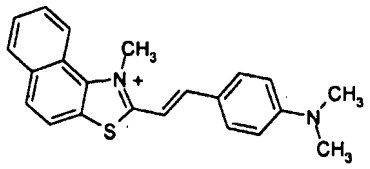
101. Use according to Claim 100 of a compound of the Formula Iv:



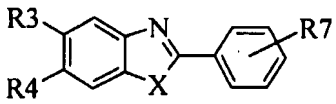
(Iv)

wherein R6 is C1-C6 alkyl.

102. Use according to Claim 101 of the compound herein designated **Compound 14** of the formula:



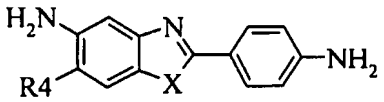
103. Use according to Claim 64 of a compound of the Formula Iw:



(Iw)

wherein R3 and R7 are -NR8R9, wherein R4, R8 and R9 are as defined in Claim 64.

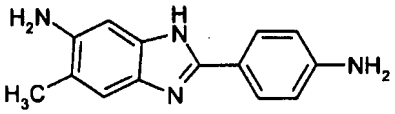
104. Use according to Claim 103 of a compound of the Formula Ix:



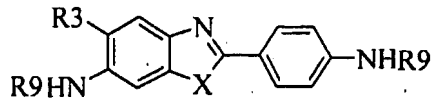
(Ix)

wherein X and R4 are as defined in Claim 64.

105. Use according to Claim 104 of the compound herein designated **Compound 15** of the formula:



106. Use according to Claim 104 of a compound of the Formula Iy:

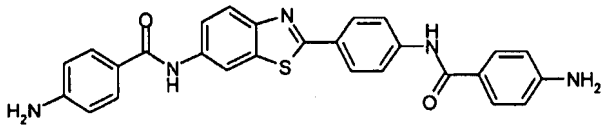


(Iy)

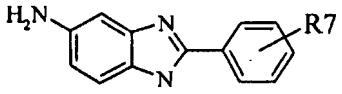
wherein X, R3 and R9 are as defined in Claim 64.

107. Use according to Claim 106 of a compound of the Formula Iy wherein X is S, and R9 is benzoyl substituted by $-NH_2$.

108. Use according to Claim 107 of the compound herein designated **Compound 16** of the formula:



109. Use according to Claim 103 of a compound of the Formula Iz:



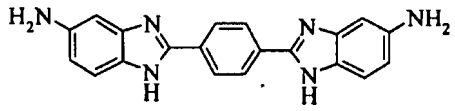
(Iz)

wherein R7 is as defined in Claim 64.

110. Use according to Claim 109 of a compound of the Formula Iz wherein R7 is selected from benzimidazol-2-yl, benzthiazol-2-yl, and benzoxazol-2-yl, said benzimidazol-2-yl, benzthiazol-2-yl, and benzoxazol-2-yl being optionally substituted by halogen, -NR8R9, $-SO_3H$, C1-C6 alkyl, C2-C6 alkenyl, C2-C7 alkanoyl, or C1-C6 alkoxy.

111. Use according to Claim 110 of a compound of the Formula Iz, wherein R7 is benzimidazolyl-2-yl, benthiazol-2-yl, or benzoxazol-2-yl substituted by $-NH_2$.

112. Use according to Claim 111 of the compound herein designated **Compound 17** of the formula:



113. Use according to any one of claims 64 to 111 for the preparation of pharmaceutical composition for inhibition of angiogenesis.

114. Use according to any one of claims 64 to 111 for the preparation of a pharmaceutical composition for treatment or inhibition of a malignant cell proliferative disease or disorder.

115. Use according to claim 113 or 114 for the preparation of a pharmaceutical composition for the treatment or inhibition of non-solid cancers, e.g hematopoietic malignancies such as all types of leukemia, e.g. acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), myelodysplastic syndrome (MDS), mast cell leukemia, hairy cell leukemia, Hodgkin's disease, non- Hodgkin's lymphomas, Burkitt's lymphoma and multiple myeloma.

116. Use according to claim 113 or 114 for the preparation of a pharmaceutical composition for the treatment or inhibition of solid tumors such as tumors in lip and oral cavity, pharynx, larynx, paranasal sinuses, major salivary glands, thyroid gland, esophagus, stomach, small intestine, colon, colorectum, anal canal, liver, gallbladder, extrahepatic bile ducts, ampulla of vater, exocrine pancreas, lung, pleural mesothelioma, bone, soft tissue sarcoma, carcinoma and malignant melanoma of the skin, breast, vulva, vagina, cervix uteri, corpus uteri, ovary, fallopian tube, gestational trophoblastic tumors, penis, prostate, testis, kidney, renal pelvis, ureter, urinary bladder, urethra, carcinoma of the eyelid, carcinoma of the conjunctiva, malignant melanoma of the conjunctiva, malignant melanoma of the uvea, retinoblastoma, carcinoma of the lacrimal gland, sarcoma of the orbit, brain, spinal cord, vascular system, hemangiosarcoma and Kaposi's sarcoma.

117. Use according to claim 113 or 114 for the preparation of a pharmaceutical composition for treating or inhibiting tumor formation, primary tumors, tumor progression or tumor metastasis.

118. Use according to any one of claims 64 to 111 for the preparation of a pharmaceutical composition for treatment of ophthalmologic disorders such as diabetic retinopathy and macular degeneration, particularly age-related macular degeneration.

119. Use according to any one of claims 64 to 111 for the preparation of a pharmaceutical composition for inhibiting or treating cell proliferative diseases or disorders such as psoriasis, hypertrophic scars, acne and sclerosis/scleroderma.

120. Use according to any one of claims 64 to 111 for the preparation of a pharmaceutical composition for inhibiting or treatment of a disease or disorder selected from polyps, multiple exostosis, hereditary exostosis, retrolental fibroplasia, hemangioma, reperfusion of gastric ulcer and arteriovenous malformation.

121. Use according to any one of claims 64 to 111 for the preparation of a pharmaceutical composition for contraception or for inducing abortion at early stages of pregnancy.

122. Use according to any one of claims 64 to 111 for the preparation of a pharmaceutical composition for treatment of or amelioration of inflammatory symptoms in any disease, condition or disorder where immune and/or inflammation suppression is beneficial.

123. Use according to claim 122, wherein said pharmaceutical composition is for treatment of or amelioration of inflammatory symptoms in the joints, musculoskeletal and connective tissue disorders.

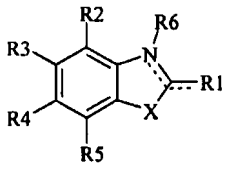
124. Use according to claim 122, wherein pharmaceutical composition is for treatment of or amelioration of inflammatory symptoms associated with hypersensitivity, allergic reactions, asthma, atherosclerosis, otitis and other otorhinolaryngological diseases, dermatitis

and other skin diseases, posterior and anterior uveitis, conjunctivitis, optic neuritis, scleritis and other immune and/or inflammatory ophthalmic diseases.

125. Use according to any one of claims 64 to 111 for the preparation of a pharmaceutical composition for treatment of or amelioration of an autoimmune disease.

126. Use according to claim 125 wherein said autoimmune disease is Eaton-Lambert syndrome, Goodpasture's syndrome, Grave's disease, Guillain-Barré syndrome, autoimmune hemolytic anemia (AIHA), hepatitis, insulin-dependent diabetes mellitus (IDDM), systemic lupus erythematosus (SLE), multiple sclerosis (MS), myasthenia gravis, plexus disorders e.g. acute brachial neuritis, polyglandular deficiency syndrome, primary biliary cirrhosis, rheumatoid arthritis, scleroderma, thrombocytopenia, thyroiditis e.g. Hashimoto's disease, Sjögren's syndrome, allergic purpura, psoriasis, mixed connective tissue disease, polymyositis, dermatomyositis, vasculitis, polyarteritis nodosa, polymyalgia rheumatica, Wegener's granulomatosis, Reiter's syndrome, Behçet's syndrome, ankylosing spondylitis, pemphigus, bullous pemphigoid, dermatitis herpetiformis, Crohn's disease or autism.

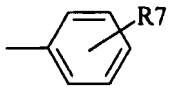
127. A method of treatment of patient suffering from a disease or disorder caused or associated with heparanase catalytic activity, which comprises administering to said patient an effective amount of a heparanase inhibitor of the general Formula I:



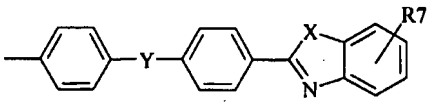
(I)

wherein

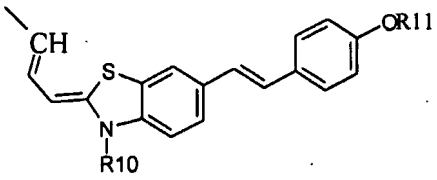
R1 is a radical selected from radicals (a)-(i):



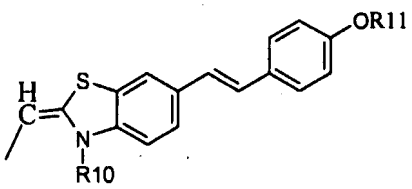
(a)


R7
X
Y
N

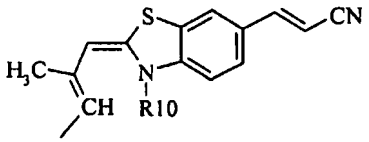
(b)


CH
S
OR11
N
R10

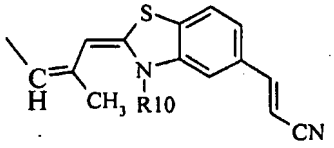
(c)


H
C
S
OR11
N
R10

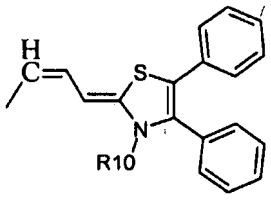
(d)


S
CN
H3C
N
CH
R10

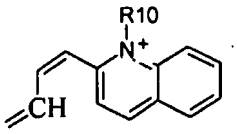
(e)


S
C
H
CH3
N
R10
CN

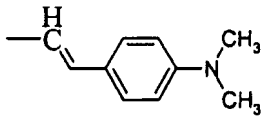
(f)


H
C
S
N
R10

(g)



(h)



(i)

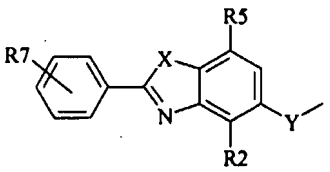
and wherein

R2 and R5 each independently represents hydrogen; halogen; -SO_3H; C1-C6 alkoxy optionally substituted by halogen or -SO_3H; C2-C6 alkenyl; C2-C7 alkanoyl; C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; C1-C6 alkylthio; or C6-C14 aryl;

R3 and R4 each independently represents hydrogen, methyl, ethyl, methoxy, ethoxy, nitro, -CH=CH-CN, or -NR8R9;

or R2 and R3 are both H and R4 and R5 together with the carbon atoms to which they are attached form a condensed benzene ring; or R4 and R5 are both H and R2 and R3 together with the carbon atoms to which they are attached form a condensed benzene ring;

or R3 is H and R4 is a radical of the formula (j):



(j)

and wherein in all formulas above:

X is NH, O or S;

Y is a direct bond, -CH_2-, -O-, -CO-, -SO-, -SO_2- or -NR' where R' is C1-C6 alkyl optionally substituted with halogen, preferably fluoro; C2-C6 alkenyl or C6-C14 aryl;

R6 is absent or is C1-C6 alkyl or C2-C6 alkenyl, wherein said C1-C6 alkyl may optionally be substituted at the terminal carbon atom by –NR8R9 or -COOR, where R is H, C1-C6 alkyl, C2-C6 alkenyl or C6-C14 aryl;

R7 is hydrogen or at least one group selected from (i) halogen; (ii) nitro; (iii) -NR8R9; (iv) $-SO_3H$; (v) -OR12; (vi) -SR12; (vii) C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; (viii) C2-C6 alkenyl; (ix) C2-C7 alkanoyl; (x) C6-C14 aryl; (xi) –N=N-R" where R" is heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S and being optionally substituted by at least one radical selected from -OH, -COOH or $-SO_3H$; (xii) benzimidazol-2-yl; (xiii) benzthiazol-2-yl; or (xiv) benzoxazol-2-yl, said radicals (xii), (xiii) and (xiv) being optionally substituted by at least one radical selected from halogen, -NR8R9, $-SO_3H$, C1-C6 alkyl, C2-C6 alkenyl, C2-C7 alkanoyl, or C1-C6 alkoxy;

R8 and R9 each independently represents hydrogen or C1-C6 alkyl, or R8 is H and R9 is C2-C7 alkanoyl or C7-C15 aroyl optionally substituted by oxo, $-SO_3H$, -COOH, and/or $-NH_2$; or the radicals R8 and R9, together with the N atom to which they are attached, form a saturated 5-7 membered heterocyclic ring optionally containing at least one further heteroatom selected from O, S and/or N, said further N atom being optionally substituted by C1-C6 alkyl;

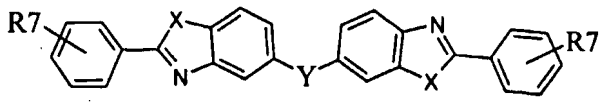
R10 is hydrogen; C1-C6 alkyl optionally substituted at the terminal carbon atom by -COOR wherein R is H, C1-C6 alkyl, C2-C6 alkenyl or aryl; or C2-C6 alkenyl;

R11 is C1-C6 alkyl optionally substituted by fluoro; C1-C6 alkoxy; C1-C6 alkylthio; or -COOR wherein R is H, C1-C6 alkyl, C2-C6 alkenyl, or aryl;

R12 is C1-C6 alkyl or C2-C6 alkenyl;

and wherein the dotted lines indicate either a double bond stretching from the carbon atom at the 2 position of the benz-1,3-azole ring to the N atom at the ring in which case said N atom is positively charged when R6 is present, or the dotted line represents a double bond stretching from the carbon atom at the 2 position of the benz-1,3-azole ring to the first carbon atom of R1, or a pharmaceutically acceptable salt thereof.

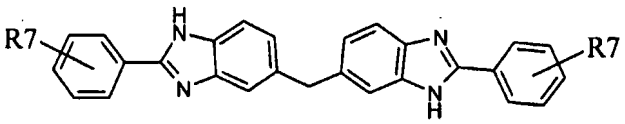
128. A method according to Claim 127 which comprises administering a compound of the Formula Ia:



(Ia)

wherein X, Y and R7 are as defined in Claim 127.

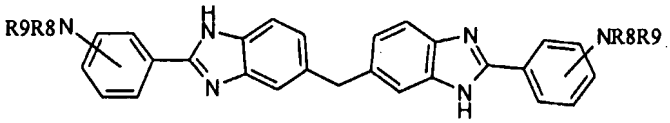
129. A method according to Claim 128 which comprises administering a compound of the Formula Ib:



(Ib)

wherein R7 is as defined in Claim 127.

130. A method according to Claim 128 which comprises administering a compound of the Formula Ic:

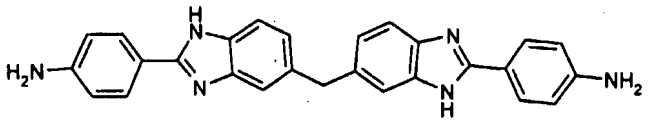


(Ic)

wherein R8 and R9 are as defined in Claim 127 and the phenyl radicals may be substituted by R7 is hydrogen or at least one group selected from (i) halogen; (ii) nitro; (iii) -NR8R9; (iv) $-SO_3H$; (v) -OR12; (vi) -SR12; (vii) C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; (viii) C2-C6 alkenyl; (ix) C2-C7 alkanoyl; (x) C6-C14 aryl; (xi) –N=N-R" where R" is heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S and being optionally substituted by at least one radical selected from -OH, -COOH or $-SO_3H$;

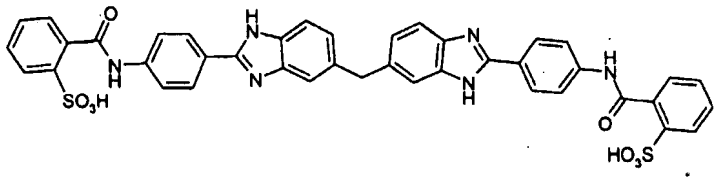
and R12 is C1-C6 alkyl or C2-C6 alkenyl.

131. A method according to Claim 130 which comprises administering the compound herein designated **Compound 1** of the formula:

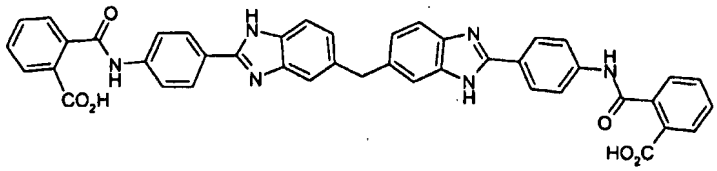


132. 114. A method according to Claim 113 which comprises administering a compound of the Formula Ic wherein R8 is H and R9 is benzoyl substituted at the ortho-position by -SO_3H or -COOH, or R9 is a 9-oxo-fluoren-3-oyl radical.

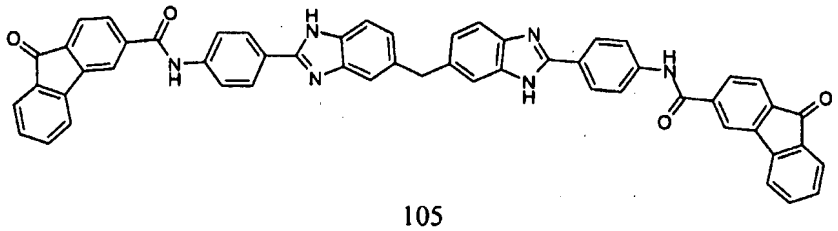
133. A method according to Claim 132 which comprises administering the compound herein designated **Compound 2** of the formula:



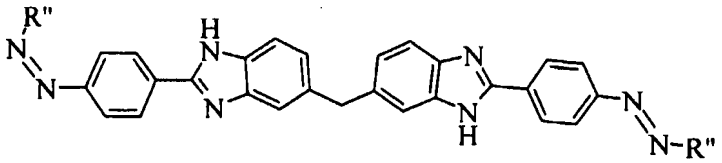
134. A method according to Claim 132 which comprises administering the compound herein designated **Compound 3** of the formula:



135. A method according to Claim 132 which comprises administering the compound herein designated **Compound 4** of the formula:



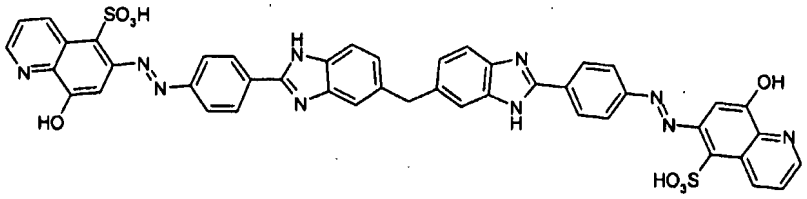
136. A method according to Claim 129 which comprises administering a compound of the Formula Id:



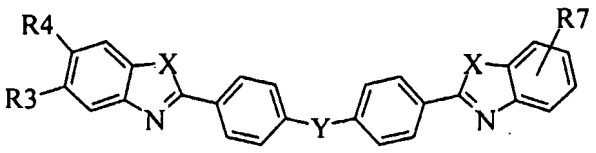
(Id)

wherein R" is a heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S and being optionally substituted by -OH, -COOH and/or $-SO_3H$.

137. A method according to Claim 136 which comprises administering the compound herein designated **Compound 5** of the formula:



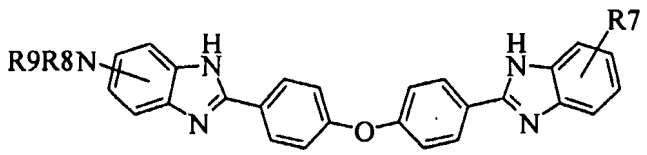
138. A method according to Claim 127 which comprises administering a compound of the Formula Ie:



(Ie)

wherein X, Y, R3, R4 and R7 are as defined in Claim 127.

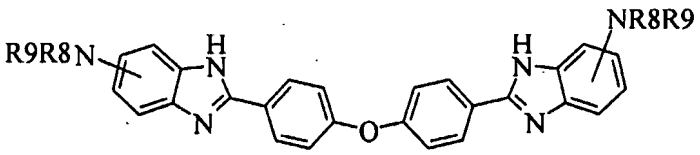
139. A method according to Claim 138 which comprises administering a compound of the Formula If:



(If)

wherein R7, R8 and R9 are as defined in Claim 127.

140. A method according to Claim 138 which comprises administering a compound of the Formula Ig:

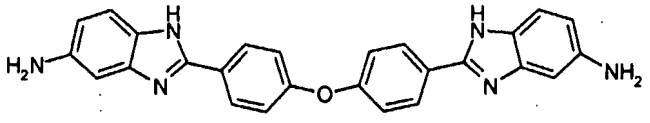


(Ig)

wherein R8 and R9 are as defined in Claim 127 and the phenyl radicals may be substituted by (i) halogen; (ii) nitro; (iii) -NR8R9; (iv) -SO_3H; (v) -OR12; (vi) -SR12; (vii) C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; (viii) C2-C6 alkenyl; (ix) C2-C7 alkanoyl; or (x) C6-C14 aryl;

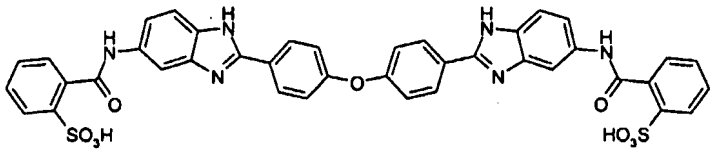
and R12 is C1-C6 alkyl or C2-C6 alkenyl.

141. A method according to Claim 140 which comprises administering the compound herein designated **Compound 6** of the formula:

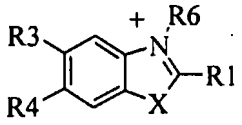


142. A method according to Claim 140 which comprises administering a compound of the Formula Ig wherein R8 is H and R9 is benzoyl substituted at the ortho-position by -SO_3H.

143. A method according to Claim 142 which comprises administering the compound herein designated **Compound 7** of the formula:



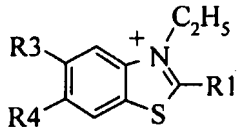
144. A method according to Claim 127 comprising a which comprises administering of the Formula Ih:



(Ih)

wherein X, R1, R3, and R4 are as defined in Claim 127 and R6 is C1-C6 alkyl.

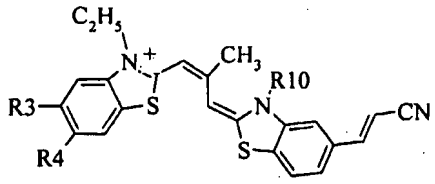
145. A method according to Claim 144 which comprises administering a compound of the Formula Ii:



(Ii)

wherein R1, R3 and R4 are as defined in Claim 127.

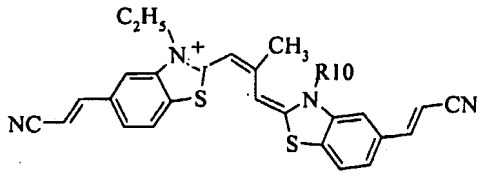
146. A method according to Claim 145 which comprises administering a compound of the Formula Ij:



(Ij)

wherein R3, R4 and R10 are as defined in Claim 127.

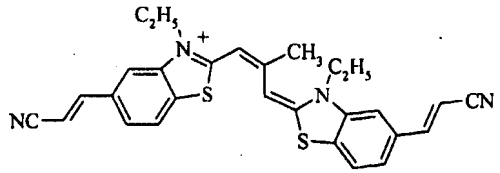
147. A method according to Claim 146 which comprises administering a compound of the Formula Ik:



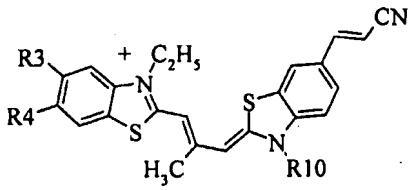
(Ik)

wherein R10 is as defined in Claim 127.

148. A method according to Claim 147 which comprises administering the compound herein designated **Compound 8** of the formula:



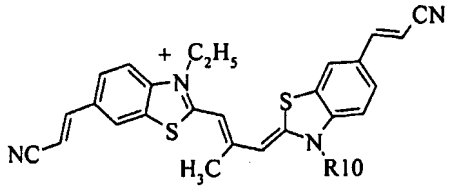
149. A method according to Claim 145 which comprises administering a compound of the Formula II:



(II)

wherein R3, R4 and R10 are as defined in Claim 127.

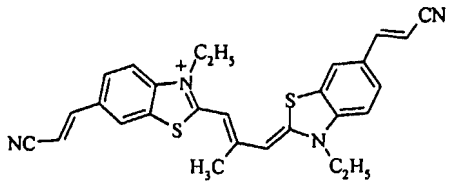
150. A method according to Claim 149 which comprises administering a compound of the Formula Im:



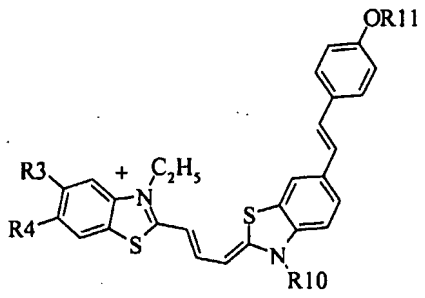
(Im)

wherein R10 is as defined in Claim 127.

151. A method according to Claim 150 which comprises administering the compound herein designated **Compound 9** of the formula:



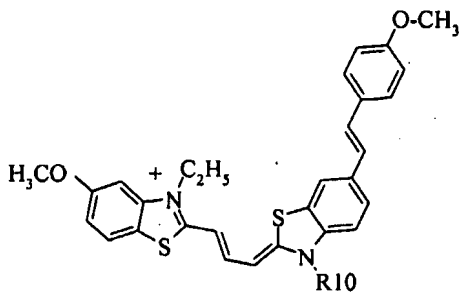
152. A method according to Claim 145 which comprises administering a compound of the Formula In:



(In)

wherein R3, R4, R10 and R11 are as defined in Claim 127.

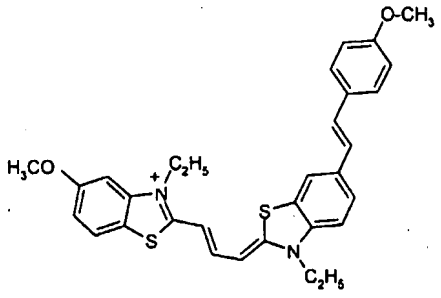
153. A method according to Claim 152 which comprises administering a compound of the Formula Io:



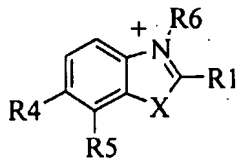
(Io)

wherein R10 is as defined in Claim 127.

154. A method according to Claim 153 which comprises administering the compound herein designated **Compound 10** of the formula:



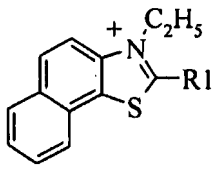
155. A method according to Claim 127 which comprises administering a compound of the Formula Ip:



(Ip)

wherein X, R1, R4, R5 and R6 are as defined in Claim 127.

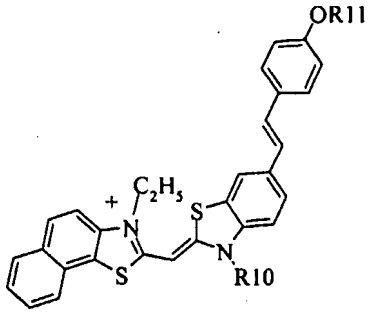
156. A method according to Claim 155 which comprises administering a compound of the Formula Iq:



(Iq)

wherein R1 is as defined in Claim 127.

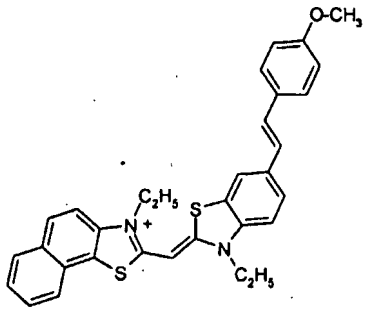
157. A method according to Claim 156 which comprises administering a compound of the Formula Ir:



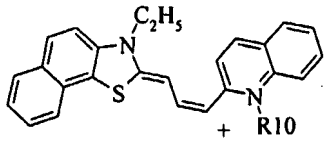
(Ir)

wherein R10 and R11 are as defined in Claim 127.

158. A method according to Claim 157 which comprises administering the compound herein designated **Compound 11** of the formula:



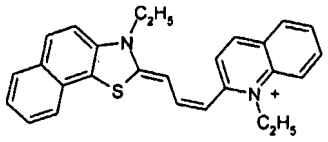
159. A method according to Claim 127 which comprises administering a compound of the Formula Is:



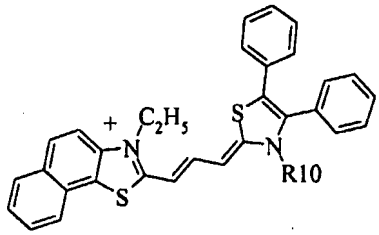
(Is)

wherein R10 is as defined in Claim 127.

160. A method according to Claim 159 which comprises administering the compound herein designated **Compound 12** of the formula:



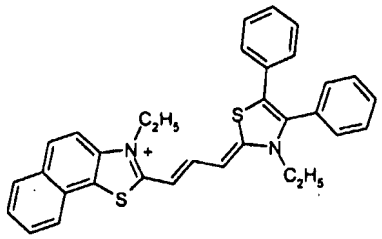
161. A method according to Claim 155 which comprises administering a compound of the Formula It:



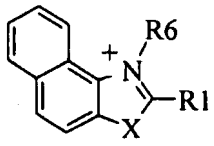
(It)

wherein R10 is as defined in Claim 127.

162. A method according to Claim 161 which comprises administering the compound herein designated **Compound 13** of the formula:



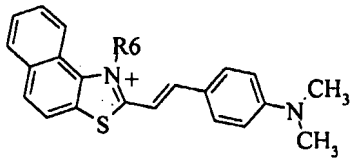
163. A method according to Claim 127 which comprises administering a compound of the Formula Iu:



(Iu)

wherein X, R1 and R6 are as defined in Claim 127.

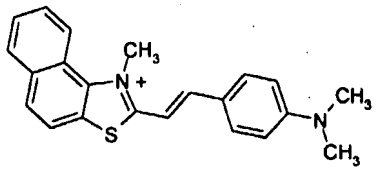
164. A method according to Claim 163 which comprises administering a compound of the Formula Iv:



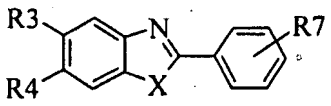
(Iv)

wherein R6 is C1-C6 alkyl.

165. A method according to Claim 164 which comprises administering the compound herein designated **Compound 14** of the formula:



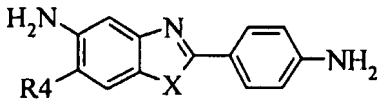
166. A method according to Claim 127 which comprises administering a compound of the Formula Iw:



(Iw)

wherein R3 and R7 are -NR8R9, wherein R4, R8 and R9 are as defined in Claim 127.

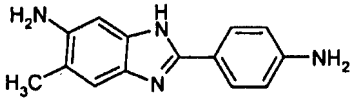
167. A method according to Claim 166 which comprises administering a compound of the Formula Ix:



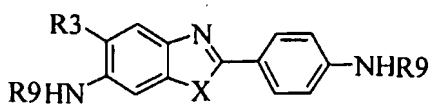
(Ix)

wherein X and R4 are as defined in Claim 127.

168. A method according to Claim 167 which comprises administering the compound herein designated **Compound 15** of the formula:



169. A method according to Claim 167 which comprises administering a compound of the Formula Iy:

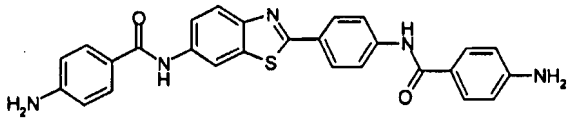


(Iy)

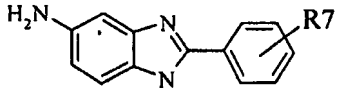
wherein X, R3 and R9 are as defined in Claim 127.

170. A method according to Claim 169 which comprises administering a compound of the Formula Iy wherein X is S, and R9 is benzoyl substituted by -NH_2.

171. A method according to Claim 170 which comprises administering the compound herein designated **Compound 16** of the formula:



172. A method according to Claim 166 which comprises administering a compound of the Formula Iz:

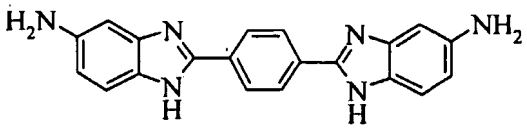


(Iz)

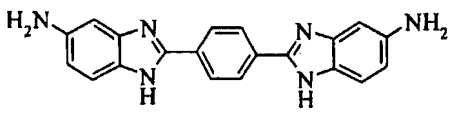
wherein R7 is as defined in Claim 127.

173. A method according to Claim 172 comprising a compound of the Formula Iz wherein R7 is selected from benzimidazol-2-yl, benzthiazol-2-yl, and benzoxazol-2-yl, said benzimidazol-2-yl, benzthiazol-2-yl, and benzoxazol-2-yl being optionally substituted by halogen, -NR8R9, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, C2-C7 alkanoyl, or C1-C6 alkoxy.

174. A method according to Claim 173 comprising a compound of the Formula Iz, wherein R7 is benzimidazolyl-2-yl, benthiazol-2-yl, or benzoxazol-2-yl substituted by -NH_2.



175. A method according to Claim 174 which comprises administering the compound herein designated **Compound 17** of the formula:



176. A method according to any one of claims 127 to 175 for inhibition of angiogenesis.

177. A method according to any one of claims 127 to 175 for treatment or inhibition of a malignant cell proliferative disease or disorder.

178. A method according to claim 176 or 177 for the treatment or inhibition of a non-solid cancer, e.g a hematopoietic malignancy such as any type of leukemia, e.g. acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), myelodysplastic syndrome (MDS), mast cell leukemia, hairy cell leukemia, Hodgkin's disease, non- Hodgkin's lymphomas, Burkitt's lymphoma and multiple myeloma.

179. A method according to claim 176 or 177 for the treatment or inhibition of solid tumors such as tumors in lip and oral cavity, pharynx, larynx, paranasal sinuses, major salivary glands, thyroid gland, esophagus, stomach, small intestine, colon, colorectum, anal canal, liver, gallbladder, extrahepatic bile ducts, ampulla of vater, exocrine pancreas, lung, pleural mesothelioma, bone, soft tissue sarcoma, carcinoma and malignant melanoma of the skin, breast, vulva, vagina, cervix uteri, corpus uteri, ovary, fallopian tube, gestational trophoblastic tumors, penis, prostate, testis, kidney, renal pelvis, ureter, urinary bladder, urethra, carcinoma of the eyelid, carcinoma of the conjunctiva, malignant melanoma of the conjunctiva, malignant melanoma of the uvea, retinoblastoma, carcinoma of the lacrimal gland, sarcoma of the orbit, brain, spinal cord, vascular system, hemangiosarcoma and Kaposi's sarcoma.

180. A method according to claim 178 or 179 for treating or inhibiting tumor formation, primary tumors, tumor progression or tumor metastasis.

181. A method according to any one of claims 127 to 175 for treatment of ophthalmologic disorders such as diabetic retinopathy and macular degeneration, particularly age-related macular degeneration.

182. A method according to any one of claims 127 to 175 for inhibiting or treating cell proliferative diseases or disorders such as psoriasis, hypertrophic scars, acne and sclerosis/scleroderma.

183. A method according to any one of claims 127 to 175 for inhibiting or treatment of a disease or disorder selected from polyps, multiple exostosis, hereditary exostosis, retrolental fibroplasia, hemangioma, reperfusion of gastric ulcer and arteriovenous malformation.

184. A method according to any one of claims 127 to 175 for contraception or for inducing abortion at early stages of pregnancy.

185. A method according to any one of claims 127 to 175 for treatment of or amelioration of inflammatory symptoms in any disease, condition or disorder where immune and/or inflammation suppression is beneficial.

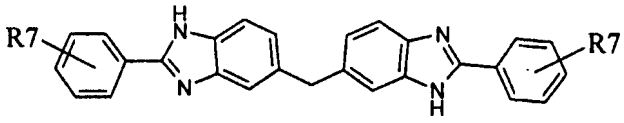
186. A method according to claim 185, for treatment of or amelioration of inflammatory symptoms in the joints, musculoskeletal and connective tissue disorders.

187. A method according to claim 185, for treatment of or amelioration of inflammatory symptoms associated with hypersensitivity, allergic reactions, asthma, atherosclerosis, otitis and other otorhinolaryngological diseases, dermatitis and other skin diseases, posterior and anterior uveitis, conjunctivitis, optic neuritis, scleritis and other immune and/or inflammatory ophthalmic diseases.

188. A method according to any one of claims 127 to 175 for treatment of or amelioration of an autoimmune disease.

189. A method according to claim 188 wherein said autoimmune disease is Eaton-Lambert syndrome, Goodpasture's syndrome, Grave's disease, Guillain-Barré syndrome, autoimmune hemolytic anemia (AIHA), hepatitis, insulin-dependent diabetes mellitus (IDDM), systemic lupus erythematosus (SLE), multiple sclerosis (MS), myasthenia gravis, plexus disorders e.g. acute brachial neuritis,, polyglandular deficiency syndrome, primary biliary cirrhosis, rheumatoid arthritis, scleroderma, thrombocytopenia, thyroiditis e.g. Hashimoto's disease, Sjögren's syndrome, allergic purpura, psoriasis, mixed connective tissue disease, polymyositis, dermatomyositis, vasculitis, polyarteritis nodosa, polymyalgia rheumatica, Wegener's granulomatosis, Reiter's syndrome, Behçet's syndrome, ankylosing spondylitis, pemphigus, bullous pemphigoid, dermatitis herpetiformis, Crohn's disease and autism.

190. A benz-1,3-azole of the formula Ib:



(Ib)

wherein

R7 is –NR8R9 or –N=N-R";

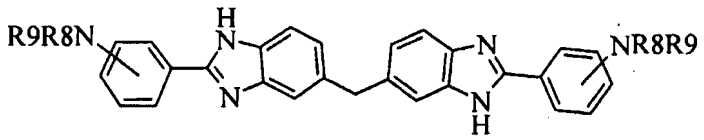
R8 and R9 each independently represents C1-C6 alkyl; or R8 is H and R9 is C2-C7 alkanoyl or C7-C15 aroyl optionally substituted by oxo, -SO_3H, -COOH, and/or -NH_2; or the radicals R8 and R9 together with the N atom to which they are attached form a saturated 5-7 membered heterocyclic ring optionally containing a further heteroatom selected from O, S and/or N, said further N atom being optionally substituted by C1-C6 alkyl;

the phenyl radicals substituted by R7 may be further substituted by (i) halogen; (ii) nitro; (iii) -NR8R9; (iv) -SO_3H; (v) -OR12; (vi) -SR12; (vii) C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; (viii) C2-C6 alkenyl; (ix) C2-C7 alkanoyl; (x) C6-C14 aryl; (xi) –N=N-R";

R" is heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S and being optionally substituted by at least one radical selected from -OH, -COOH or -SO_3H;

and R12 is C1-C6 alkyl or C2-C6 alkenyl.

191. A benzimidazole according to Claim 190 of the formula Ic:



(Ic)

wherein

R8 and R9 each independently represents C1-C6 alkyl; or R8 is H and R9 is C2-C7 alkanoyl or C7-C15 aroyl optionally substituted by oxo, -SO_3H, -COOH, and/or -NH_2; or the radicals R8 and R9 together with the N atom to which they are attached form a saturated 5-7 membered heterocyclic ring optionally containing a further heteroatom selected from O, S and/or N, said further N atom being optionally substituted by C1-C6 alkyl;

the phenyl radicals substituted by –NR8R9 may be further substituted by (i) halogen; (ii) nitro; (iii) -NR8R9; (iv) -SO_3H; (v) -OR12; (vi) -SR12; (vii) C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; (viii) C2-C6 alkenyl; (ix) C2-C7 alkanoyl; (x) C6-C14 aryl; (xi) –N=N-R";

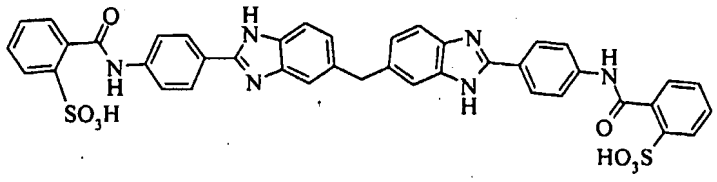
R" is heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S and being optionally substituted by at least one radical selected from -OH, -COOH or -SO_3H;

and R12 is C1-C6 alkyl or C2-C6 alkenyl.

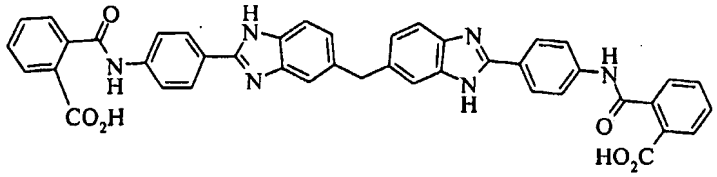
192. A benzimidazole according to Claim 191, wherein the radicals –NR8R9 are at the para-positions of the phenyl rings and wherein R8 and R9 are as defined in Claim 190.

193. A benzimidazole according to Claim 192, wherein R8 is H and R9 is benzoyl substituted at the ortho-position by $-SO_3H$ or $-COOH$, or R9 is a 9-oxo-fluoren-3-oyl radical.

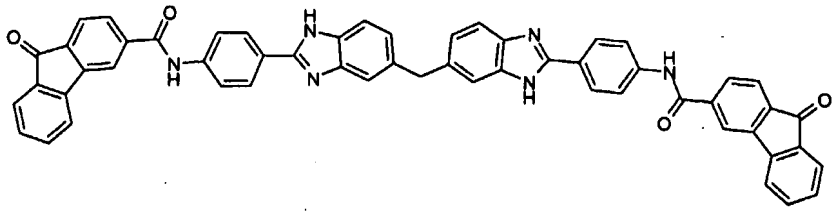
194. A benzimidazole according to Claim 193 herein designated **Compound 2** of the formula:



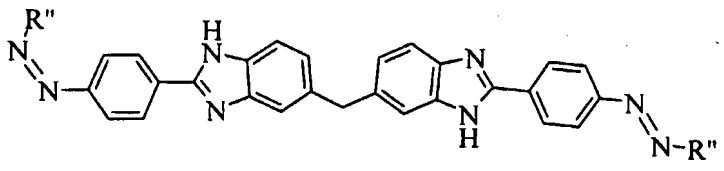
195. A benzimidazole according to Claim 193 herein designated **Compound 3** of the formula:



196. A benzimidazole according to Claim 193 herein designated **Compound 4** of the formula:



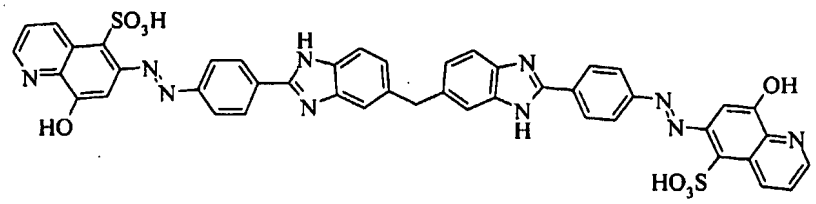
197. A benzimidazole according to Claim 190 of the formula Id:



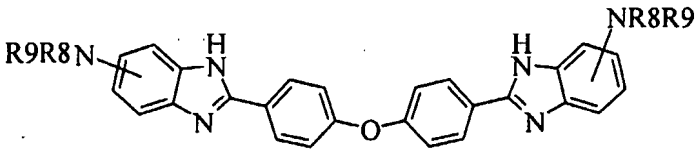
(Id)

wherein R" is heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S and being optionally substituted by -OH, -COOH and/or -SO_3H.

198. A benzimidazole according to Claim 197 herein designated **Compound 5** of the formula:



199. A benzimidazole of the formula Ig:



(Ig)

wherein

R8 and R9 each independently represents C1-C6 alkyl; or R8 is H and R9 is C2-C7 alkanoyl or C7-C15 aroyl optionally substituted by oxo, -SO_3H, -COOH, and/or -NH_2; or the radicals R8 and R9 together with the N atom to which they are attached form a saturated 5-7 membered heterocyclic ring optionally containing a further heteroatom selected from O, S and/or N, said further N atom being optionally substituted by C1-C6 alkyl;

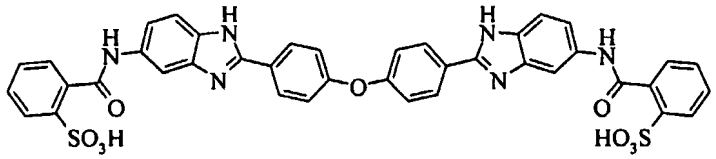
the phenyl radicals substituted by –NR8R9 may be further substituted by (i) halogen; (ii) nitro; (iii) -NR8R9; (iv) -SO_3H; (v) -OR12; (vi) -SR12; (vii) C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; (viii) C2-C6 alkenyl; (ix) C2-C7 alkanoyl; or (x) C6-C14 aryl;

and R12 is C1-C6 alkyl or C2-C6 alkenyl.

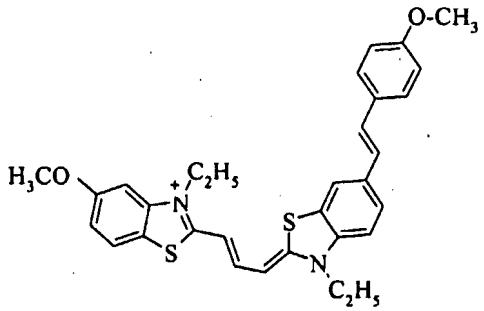
200. A benzimidazole according to Claim 199, wherein the radicals -NR8R9 are at the 5-position of the imidazole rings and R8 and R9 are as defined in Claim 199.

201. A benzimidazole according to Claim 200, wherein R8 is H and R9 is benzoyl substituted at the ortho-position by $-SO_3H$.

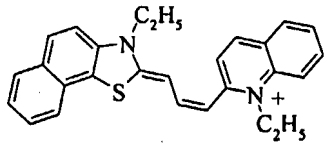
202. A benzimidazole according to Claim 201 herein designated **Compound 7** of the formula:



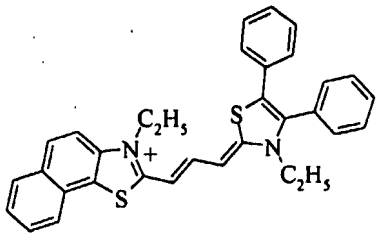
203. A benzthiazole herein designated **Compound 10** of the formula:



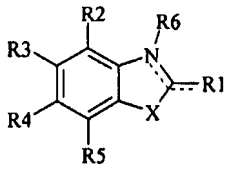
204. A benzthiazole herein designated **Compound 12** of the formula:



205. A benzthiazole herein designated **Compound 13** of the formula:



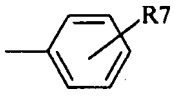
206. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one benz-1,3-azole compound of the general Formula I:



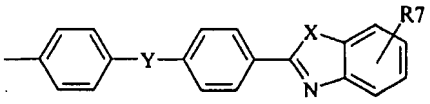
(I)

wherein

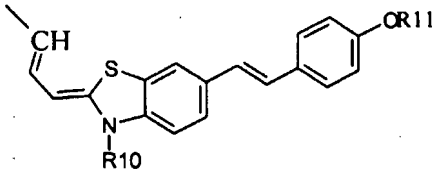
R1 is a radical selected from radicals (a)-(i):



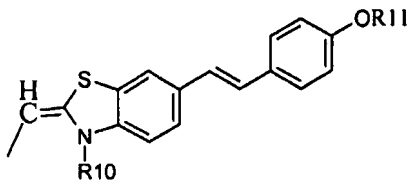
(a)



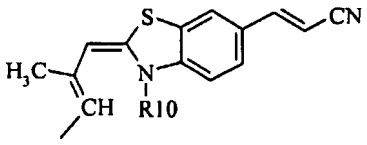
(b)



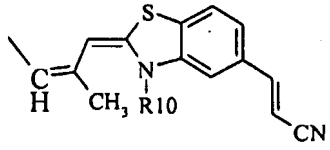
(c)


OR11
H
S
C
N
R10

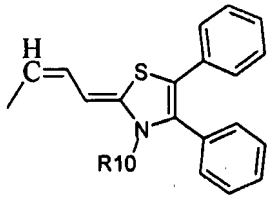
(d)


S
CN
H3C
N
CH
R10

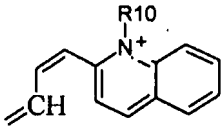
(e)


S
C
H
N
CH3
R10
CN

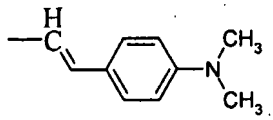
(f)


H
C
S
N
R10

(g)


R10
N+
CH

(h)


H
C
CH3
N
CH3

(i)

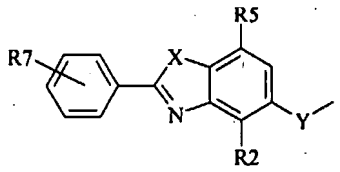
and wherein

R2 and R5 each independently represents hydrogen; halogen; -SO_3H; C1-C6 alkoxy optionally substituted by halogen or -SO_3H; C2-C6 alkenyl; C2-C7 alkanoyl; C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; C1-C6 alkylthio; or C6-C14 aryl;

R3 and R4 each independently represents hydrogen, methyl, ethyl, methoxy, ethoxy, nitro, -CH=CH-CN, or -NR8R9;

or R2 and R3 are both H and R4 and R5 together with the carbon atoms to which they are attached form a condensed benzene ring; or R4 and R5 are both H and R2 and R3 together with the carbon atoms to which they are attached form a condensed benzene ring;

or R3 is H and R4 is a radical of the formula (j):



(j)

and wherein in all formulas above:

X is NH, O or S;

Y is a direct bond, -CH_2-, -O-, -CO-, -SO-, -SO_2- or -NR' where R' is C1-C6 alkyl optionally substituted with halogen, preferably fluoro; C2-C6 alkenyl or C6-C14 aryl;

R6 is absent or is C1-C6 alkyl or C2-C6 alkenyl, wherein said C1-C6 alkyl may optionally be substituted at the terminal carbon atom by –NR8R9 or -COOR, where R is H, C1-C6 alkyl, C2-C6 alkenyl or C6-C14 aryl;

R7 is hydrogen or at least one group selected from (i) halogen; (ii) nitro; (iii) -NR8R9; (iv) -SO_3H; (v) -OR12; (vi) -SR12; (vii) C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; (viii) C2-C6 alkenyl; (ix) C2-C7 alkanoyl; (x) C6-C14 aryl; (xi) –N=N-R" where R" is heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S and being optionally substituted by at least one radical selected from -OH, -COOH or -SO_3H; (xii) benzimidazol-2-yl; (xiii) benzthiazol-2-yl; or (xiv) benzoxazol-2-yl, said radicals (xii), (xiii) and (xiv) being optionally substituted by at least one radical selected from halogen, -NR8R9, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, C2-C7 alkanoyl, or C1-C6 alkoxy;

R8 and R9 each independently represents hydrogen or C1-C6 alkyl, or R8 is H and R9 is C2-C7 alkanoyl or C7-C15 aroyl optionally substituted by oxo, $-SO_3H$, -COOH, and/or $-NH_2$; or the radicals R8 and R9, together with the N atom to which they are attached, form a saturated 5-7 membered heterocyclic ring optionally containing at least one further heteroatom selected from O, S and/or N, said further N atom being optionally substituted by C1-C6 alkyl;

R10 is hydrogen; C1-C6 alkyl optionally substituted at the terminal carbon atom by -COOR wherein R is H, C1-C6 alkyl, C2-C6 alkenyl or aryl; or C2-C6 alkenyl;

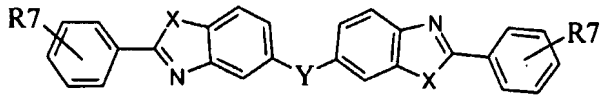
R11 is C1-C6 alkyl optionally substituted by fluoro; C1-C6 alkoxy; C1-C6 alkylthio; or -COOR wherein R is H, C1-C6 alkyl, C2-C6 alkenyl, or aryl;

R12 is C1-C6 alkyl or C2-C6 alkenyl;

and wherein the dotted lines indicate either a double bond stretching from the carbon atom at the 2 position of the benz-1,3-azole ring to the N atom at the ring in which case said N atom is positively charged when R6 is present, or the dotted line represents a double bond stretching from the carbon atom at the 2 position of the benz-1,3-azole ring to the first carbon atom of R1; and

pharmaceutically acceptable salts thereof.

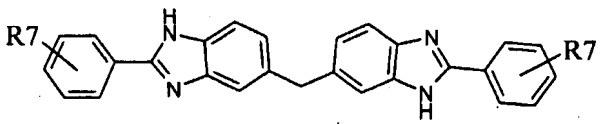
207. A pharmaceutical composition according to Claim 206 comprising a compound of the Formula Ia:



(Ia)

wherein X, Y and R7 are as defined in Claim 206.

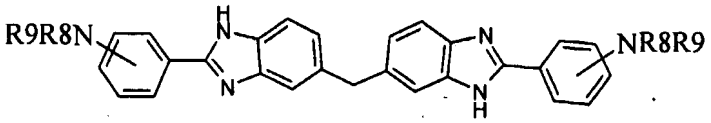
208. A pharmaceutical composition according to Claim 207 comprising a compound of the Formula Ib:



(Ib)

wherein R7 is as defined in Claim 206.

209. A pharmaceutical composition according to Claim 208 comprising a compound of the Formula Ic:

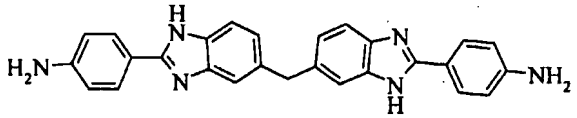


(Ic)

wherein R8 and R9 are as defined in Claim 1 and the phenyl radicals may be further substituted by (i) halogen; (ii) nitro; (iii) -NR8R9; (iv) -SO_3H; (v) -OR12; (vi) -SR12; (vii) C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; (viii) C2-C6 alkenyl; (ix) C2-C7 alkanoyl; (x) C6-C14 aryl; (xi) –N=N-R" where R" is heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S and being optionally substituted by at least one radical selected from -OH, -COOH or -SO_3H;

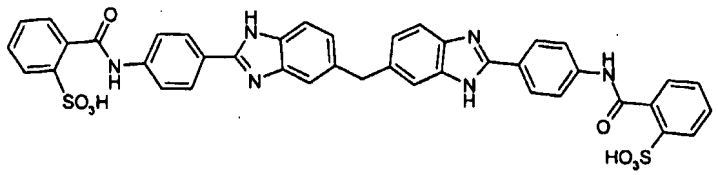
and R12 is C1-C6 alkyl or C2-C6 alkenyl.

210. A pharmaceutical composition according to Claim 209 comprising the compound herein designated **Compound 1** of the formula:

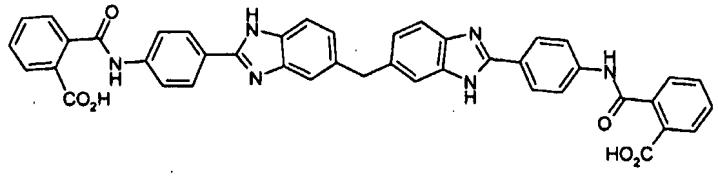


211. A pharmaceutical composition according to Claim 209 comprising a compound of the Formula Ic wherein R8 is H and R9 is benzoyl substituted at the ortho-position by -SO_3H or -COOH, or R9 is a 9-oxo-fluoren-3-oyl radical.

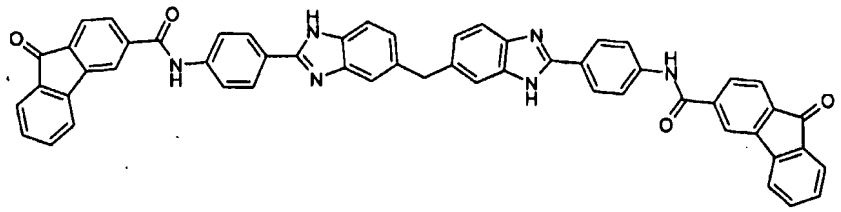
212. A pharmaceutical composition according to Claim 211 comprising the compound herein designated **Compound 2** of the formula:



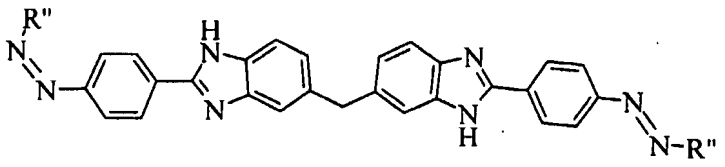
213. A pharmaceutical composition according to Claim 211 comprising the compound herein designated **Compound 3** of the formula:



214. A pharmaceutical composition according to Claim 211 comprising the compound herein designated **Compound 4** of the formula:



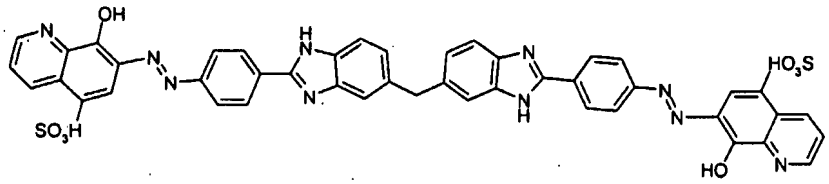
215. A pharmaceutical composition according to Claim 208 comprising a compound of the Formula Id:



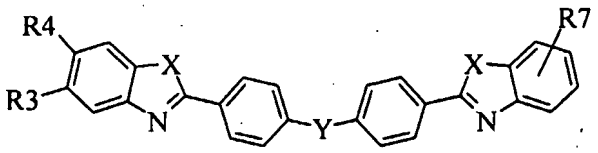
(Id)

wherein R" is a heteroaryl derived from a mono- or poly-cyclic heteroatomatic ring containing one to three heteroatoms selected from N, O and/or S and being optionally substituted by -OH, -COOH and/or -SO_3H.

216. A pharmaceutical composition according to Claim 215 comprising the compound herein designated **Compound 5** of the formula:



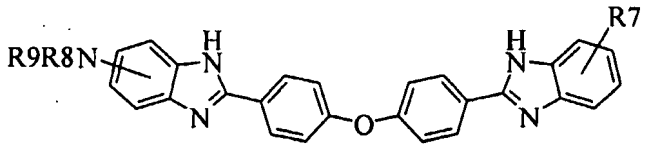
217. A pharmaceutical composition according to Claim 206 comprising a compound of the Formula Ie:



(Ie)

wherein R3 is H and R4 is –NR8R9 or R4 is H and R3 is –NR8R9, and X, Y and R7 are as defined in Claim 206.

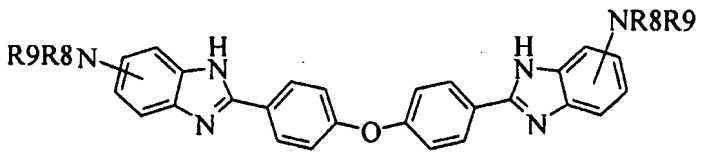
218. A pharmaceutical composition according to Claim 217 comprising a compound of the Formula If:



(If)

wherein R7, R8 and R9 are as defined in Claim 206.

219. A pharmaceutical composition according to Claim 218 comprising a compound of the Formula Ig:

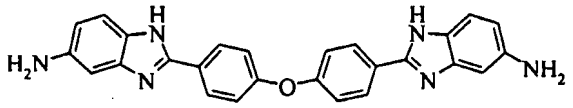


(Ig)

wherein R8 and R9 are as defined in Claim 206 and the phenyl radicals may be further substituted (i) halogen; (ii) nitro; (iii) -NR8R9; (iv) -SO_3H; (v) -OR12; (vi) -SR12; (vii) C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy; (viii) C2-C6 alkenyl; (ix) C2-C7 alkanoyl; or (x) C6-C14 aryl;

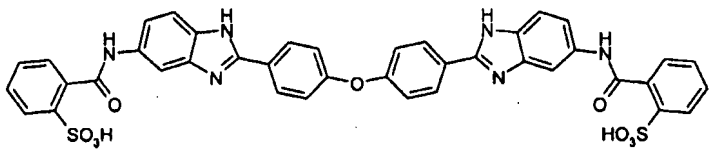
and R12 is C1-C6 alkyl or C2-C6 alkenyl.

220. A pharmaceutical composition according to Claim 219 comprising the compound herein designated **Compound 6** of the formula:

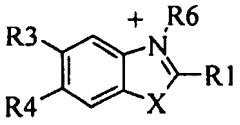


221. A pharmaceutical composition according to Claim 219 comprising a compound of the Formula Ig wherein R8 is H and R9 is benzoyl substituted at the ortho-position by -SO_3H.

222. A pharmaceutical composition according to Claim 221 comprising the compound herein designated **Compound 7** of the formula:



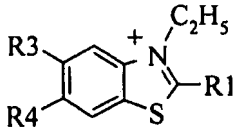
223. A pharmaceutical composition according to Claim 206 comprising a compound of the Formula Ih:



(Ih)

wherein X, R1, R3, and R4 are as defined in Claim 206 and R6 is C1-C6 alkyl.

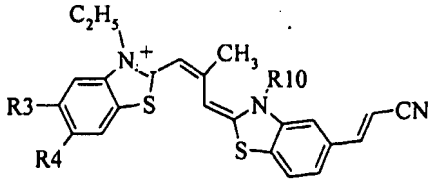
224. A pharmaceutical composition according to Claim 223 comprising a compound of the Formula Ii:



(Ii)

wherein R1, R3 and R4 are as defined in Claim 206.

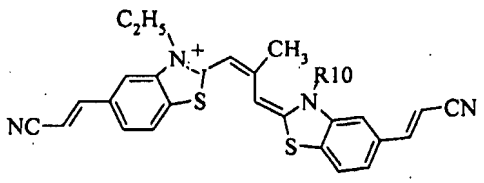
225. A pharmaceutical composition according to Claim 224 comprising a compound of the Formula Ij:



(Ij)

wherein R3, R4 and R10 are as defined in Claim 206.

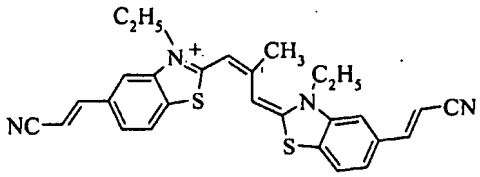
226. A pharmaceutical composition according to Claim 225 comprising a compound of the Formula Ik:



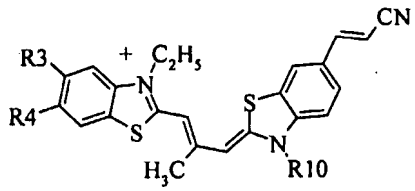
(Ik)

wherein R10 is as defined in Claim 206.

227. A pharmaceutical composition according to Claim 226 comprising the compound herein designated **Compound 8** of the formula:



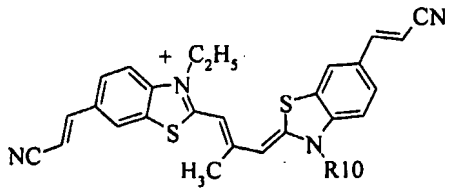
228. A pharmaceutical composition according to Claim 224 comprising a compound of the Formula II:



(II)

wherein R3, R4 and R10 are as defined in Claim 206.

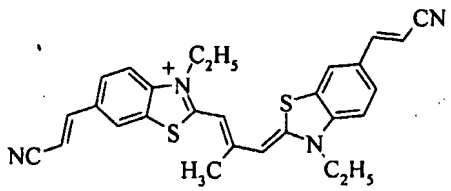
229. A pharmaceutical composition according to Claim 228 comprising a compound of the Formula Im:



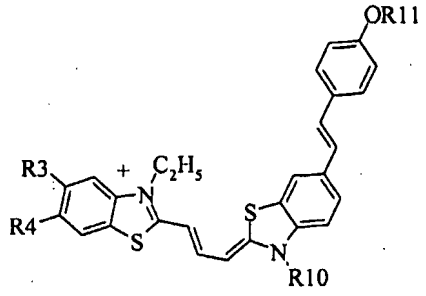
(Im)

wherein R10 is as defined in Claim 206.

230. A pharmaceutical composition according to Claim 229 comprising the compound herein designated **Compound 9** of the formula:



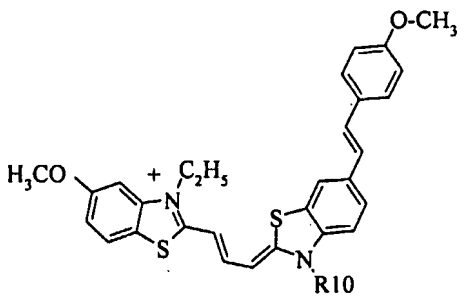
231. A pharmaceutical composition according to Claim 224 comprising a compound of the Formula In:



(In)

wherein R3, R4, R10 and R11 are as defined in Claim 206.

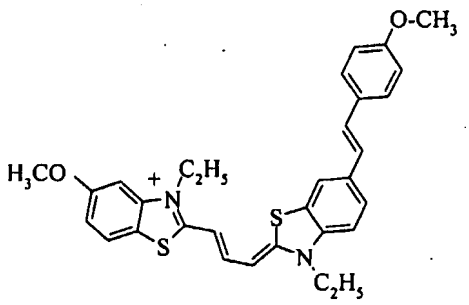
232. A pharmaceutical composition according to Claim 231 comprising a compound of the Formula Io:



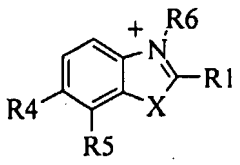
(Io)

wherein R10 is as defined in Claim 206.

233. A pharmaceutical composition according to Claim 232 comprising the compound herein designated **Compound 10** of the formula:



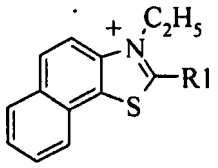
234. A pharmaceutical composition according to Claim 206 comprising a compound of the Formula Ip:



(Ip)

wherein X, R1, R4, R5 and R6 are as defined in Claim 206.

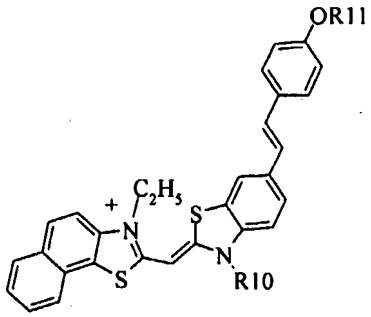
235. A pharmaceutical composition according to Claim 234 comprising a compound of the Formula Iq:



(Iq)

wherein R1 is as defined in Claim 206.

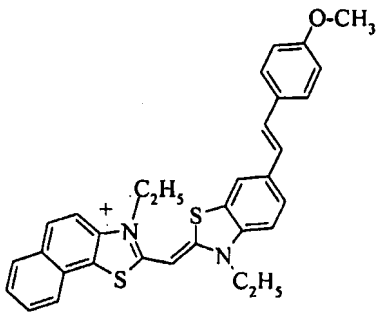
236. A pharmaceutical composition according to Claim 235 comprising a compound of the Formula Ir:



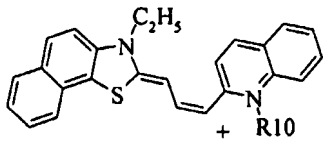
(Ir)

wherein R10 and R11 are as defined in Claim 206.

237. A pharmaceutical composition according to Claim 236 comprising the compound herein designated **Compound 11** of the formula:



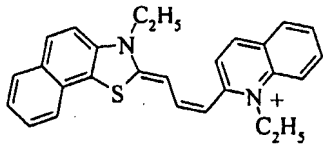
238. A pharmaceutical composition according to Claim 206 comprising a compound of the Formula Is:



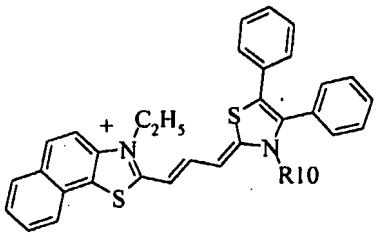
(Is)

wherein R10 is as defined in Claim 206.

239. A pharmaceutical composition according to Claim 238 comprising the compound herein designated **Compound 12** of the formula:



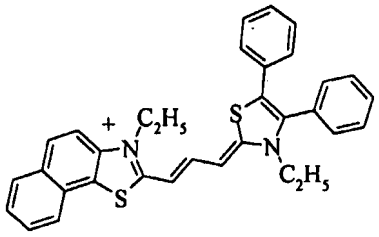
240. A pharmaceutical composition according to Claim 235 comprising a compound of the Formula It:



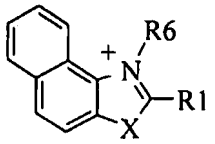
(It)

wherein R10 is as defined in Claim 206.

241. A pharmaceutical composition according to Claim 240 comprising the compound herein designated **Compound 13** of the formula:



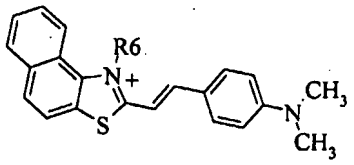
242. A pharmaceutical composition according to Claim 206 comprising a compound of the Formula Iu:



(Iu)

wherein X, R1 and R6 are as defined in Claim 206.

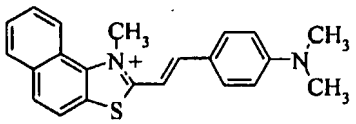
243. A pharmaceutical composition according to Claim 242 comprising a compound of the Formula Iv:



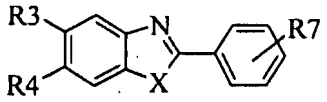
(Iv)

wherein R6 is C1-C6 alkyl.

244. A pharmaceutical composition according to Claim 243 comprising the compound herein designated **Compound 14** of the formula:



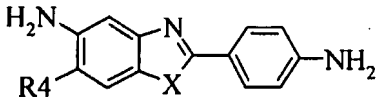
245. A pharmaceutical composition according to Claim 206 comprising a compound of the Formula Iw:



(Iw)

wherein R3 and R7 are -NR8R9, wherein R4, R8 and R9 are as defined in Claim 206.

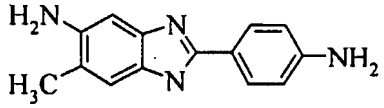
246. A pharmaceutical composition according to Claim 245 comprising a compound of the Formula Ix:



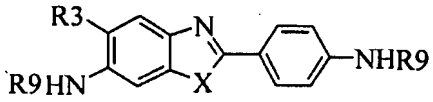
(Ix)

wherein X and R4 are as defined in Claim 206.

247. A pharmaceutical composition according to Claim 246 comprising the compound herein designated **Compound 15** of the formula:



248. A pharmaceutical composition according to Claim 246 comprising a compound of the Formula Iy:

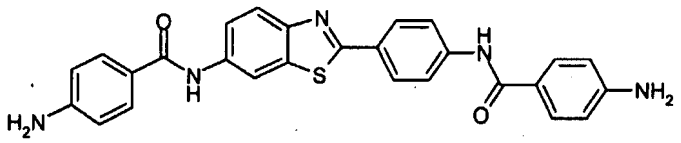


(Iy)

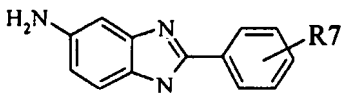
wherein X, R3 and R9 are as defined in Claim 206.

249. A pharmaceutical composition according to Claim 248 comprising a compound of the Formula Iy wherein X is S, and R9 is benzoyl substituted by -NH_2.

250. A pharmaceutical composition according to Claim 249 comprising the compound herein designated **Compound 16** of the formula:



251. A pharmaceutical composition according to Claim 245 comprising a compound of the Formula Iz:



(Iz)

wherein R7 is as defined in Claim 206.

252. A pharmaceutical composition according to Claim 251 comprising a compound of the Formula Iz wherein R7 is selected from benzimidazol-2-yl, benzthiazol-2-yl, and benzoxazol-2-yl, said benzimidazol-2-yl, benzthiazol-2-yl, and benzoxazol-2-yl being optionally substituted by halogen, -NR8R9, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, C2-C7 alkanoyl, or C1-C6 alkoxy.

253. A pharmaceutical composition according to Claim 252 comprising a compound of the Formula Iz, wherein R7 is benzimidazolyl-2-yl, benthiazol-2-yl, or benzoxazol-2-yl substituted by -NH_2.

254. A pharmaceutical composition according to Claim 253 comprising the compound herein designated **Compound 17** of the formula: